Handbook of Drug-Eluting Stents

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Editors

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32. Dexamethasone: mode of action, preclinical, and clinical studies

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INTRODUCTION

In-stent restenosis, mainly caused by an abundant neointimal hyperplasia, remains the major limitation of coronary stent implantation. Mural thrombi, inflammatory response, smooth muscle cell (SMC) dedifferentiation, migration and proliferation, and furthermore extracellular matrix formation, all participate to the pathogenesis of neointimal hyperplasia. Changing any of these factors might have an impact on neointimal hyperplasia. Systemic delivery of medications has been unsuccessful in reducing restenosis. Local drug delivery via infusion devices introduced additional complexity to the procedure and may not deliver sufficient medication to the site of the injury. It also resulted in insufficient results. Drug-eluting stents, however, can deliver an adequate amount of medication to the site of injury for a sufficient period of time and have been proposed as an alternative approach to decrease neointimal hyperplasia. Some preliminary studies have shown very promising results [1,2].

MODE OF ACTION OF DEXAMETHASONE

The role of inflammation in atherosclerosis and restenosis has been widely discussed in recent literature [3–6]. Inflammation is an inevitable consequence of angioplasty, as injury to the vessel wall and the introduction of a foreign object (stent) both elicit an adverse host response. While the injury is somewhat dictated by the procedure used or the type of stent selected, the subsequent host response can be controlled by the use of anti-inflammatory compounds. The corticosteroids, including dexamethasone, methylprednisolone, and hydrocortisone, are a well-documented group of steroidal drugs. Indeed, dexamethasone itself has been approved by the FDA since 1958 and is extensively used in inflammation management. In animal models, local delivery of such corticosteroids has been shown to reduce inflammation markers caused by percutaneous transluminal coronary angioplasty (PTCA) and stenting procedures [7,8] (Figure 32.1).

The inflammatory response consists of both innate (nonspecific) and acute (specific) reactions. The innate reactions are induced by release of plasma and cell-derived mediators. Increased vessel permeability results in the exudation of fluid into the injured tissue, which contains components from the complement, coagulation, fibrinolytic, and kinin cascades that stimulate the release of a host of chemical inflammatory mediators; cellular events are induced by endothelial, mast and macrophage cells present in the tissue, and platelets and leukocytes from the blood. The acute reactions are a consequence of more specific activation of B and T lymphocytes by antigens that migrate to the lymph nodes.

Dexamethasone is a glucocorticoid that readily crosses target cell membranes (1) and binds to the intracytoplasmic glucocorticoid receptor complex (2), causing the dissociation of two protein subunits (3) and the subsequent activation of the complex [9]. The activated complex can migrate to the nucleus where it binds to Glucocorticoid Response Elements

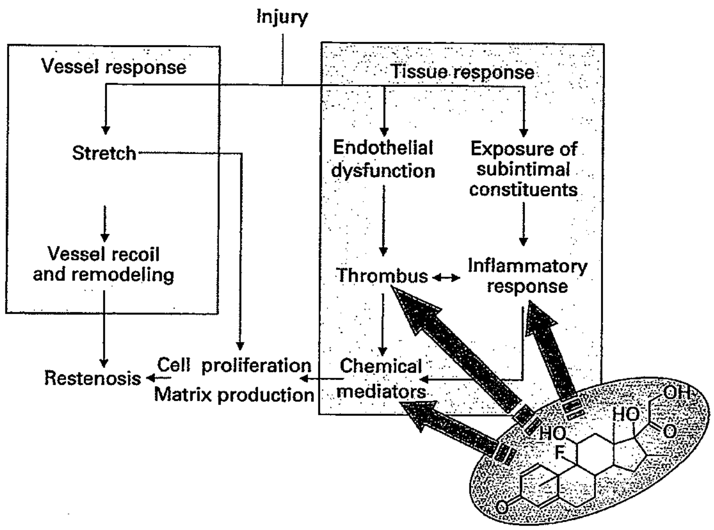

Figure 32.1

Targets for corticosteroids in response to vessel injury.

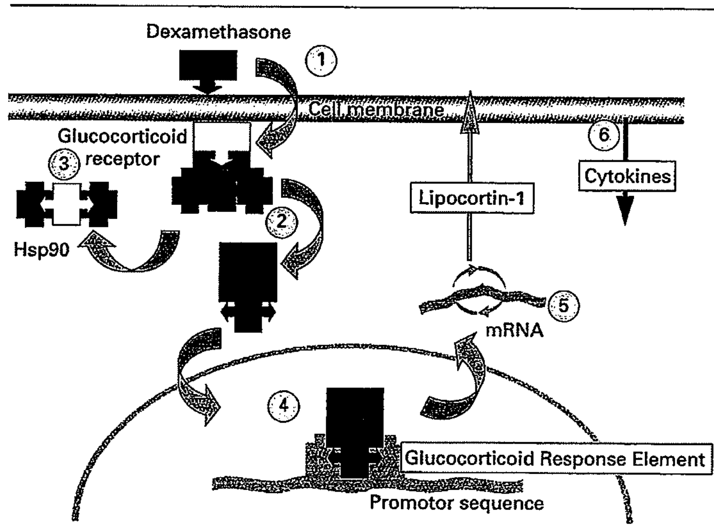

Figure 32.2

Molecular mode of action for dexamethasone.

(GRE) (4) (receptors) in the DNA, resulting in the modification of protein synthesis (5), thereby inhibiting inflammatory responses (Figure 32.2). A transcription Activator Protein (AP-1) can also interact with the activated complex to bring about modification of collagenase and interleukins. Cytokines are affected through a similar process (6) as their genes

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possess several GREs [10]. Glucocorticoids also have an effect on the prostaglandin synthesis pathway, which is responsible for production of the lipid inflammatory mediators. The primary anti-inflammatory action is inhibition of the induction of cyclo-oxygenase-2 (COX-2) [11] by the AP-1–glucocorticoid complex. COX-2 is generally undetectable in most tissues but increases its expression during acute inflammation or in response to cytokine stimulation-producing prostaglandins found at sites of inflammation.

PRECLINICAL EVALUATION OF STENT-MEDIATED DELIVERY OF CORTICOSTEROIDS

Continuous administration of hydrocortisone or dexamethasone, either systemically or from periadventitial polymers, has been shown to reduce reactive intimal hyperplasia in rabbit and rat models of restenosis [7,12]. Evidence to support the inhibitory effects of corticosteroids to the foreign body response when delivered from a stent were described in a study of methyl prednisolone impregnated in Wiktor stents coated with polyorganophosphazene [13], and stents coated with a fluorinated polymethacrylate by a variety of methods [14]. Local drug delivery of dexamethasone from a poly(L-lactic acid) coated tantalum wire stent in a porcine model did not result in a reduction of intimal hyperplasia [8]. The positive effects of the drug may however, have been offset by the adverse effects of the polymer, as it has been shown that biodegradable polymers can cause increased inflammation and neointimal thickening in a porcine model [15]. Indeed, when Strecker stents, coated with pure polylactide or a polylactide copolymer containing a 10-fold higher dose of dexamethasone than the previous study, were evaluated in a canine femoral model, significantly less neointimal hyperplasia compared to uncoated stents was reported [16]. Furthermore, only 20% of the dexamethasone was released over the first 24 hours, with sustained delivery over 40 days. Adverse effects induced by polymer coatings are not however, limited to biodegradable materials [15]. Analysis of the preclinical data from three separate porcine studies of sirolimus delivery from polymer-coated stents shows that the powerful effects of the drug are necessary to overcome the increase in neointimal area induced by the polymer alone (Figure 32.3) [17].

In order to separate the anti-inflammatory effects of the drug from potential adverse reactions to the polymer coatings employed as delivery vehicles, preclinical studies in a porcine coronary model were performed using the Bio*divYsio* Matrix LO drug delivery stent, which has been shown in many studies to cause no coating-related inflammatory reaction [18–21]. The stent is characterized by a biocompatible coating capable of absorbing a range of therapeutic agents [22] for subsequent delivery to the vessel wall. Drug loadings of 0.9 $\mu g/mm^2$ of dexamethasone (LDD) and ~2.5 $\mu g/mm^2$ for both dexamethasone (HDD) and methyl prednisolone (MP) were used in this preclinical study. Results of this study

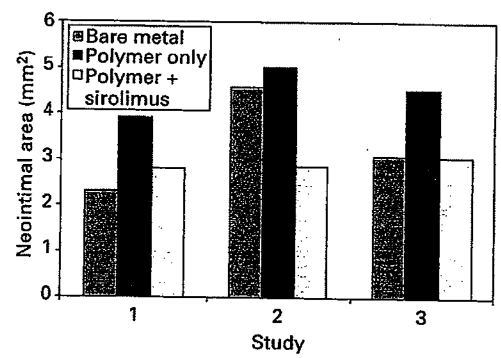

Figure 32.3

Comparison of neointimal area for bare metal, polymer coated, and polymer coated + sirolimus stents in preclinical studies reported by Cordis [17].

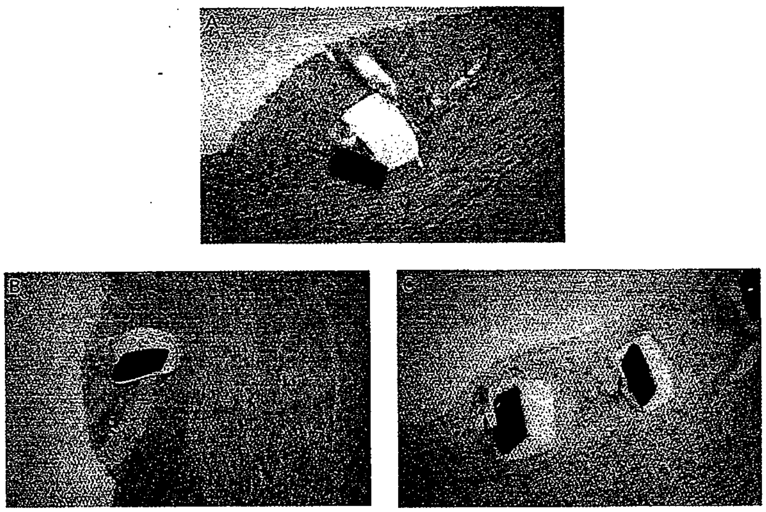

Figure 32.4

Photomicrograph of a vessel segment stented with (A) a bare stent, (B) a dexamethasone-loaded stent, and (C) a methylprednisolone-loaded stent, all at 5-day follow-up. The histolymphocytic reaction surrounding the stent filaments was reduced by the local steroid delivery in (B) and (C) (hematoxylin and eosin stain).

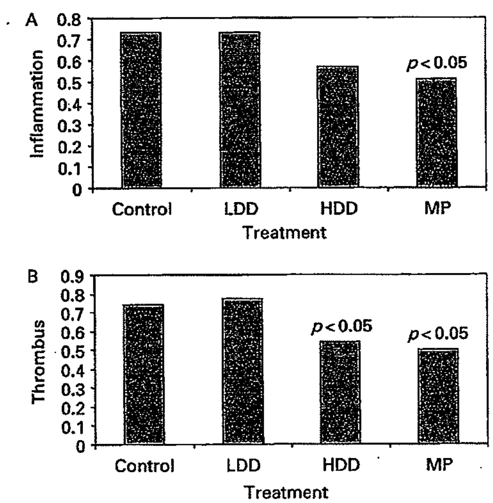

Figure 32.5

Effects of corticosteroid delivery from the Bio*divYsio* Matrix LO stent on (A) inflammation and (B) thrombus.

showed only scarce leukocytes, macrophages, and giant cells in the neointima in all samples studied, supporting other studies [19] that show PC-coated stents demonstrate a minimal inflammatory response at 5 days follow-up, even in an oversized injury model (Figure 32.4). Even with the lower than normal results obtained in the control stents, it was observed that local release of dexamethasone or methyl prednisolone further decreased the severity of the inflammatory response, the inflammatory score of the methyl prednisolone group being significantly lower than that of the control group (Figure 32.5A).

Steroids have also been shown to inhibit the formation of platelet-activating factor and may exert an antiplatelet effect [23]. The occurrence of thrombus surrounding the stent filaments in the dexamethasone and methyl prednisolone groups was also lower than the control (Figure 32.5B). As the early inflammatory

Table 32.

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$n = 12$, *$p <$

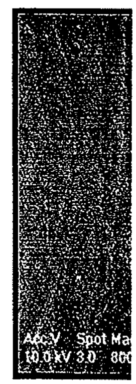

Figure 32.6

Scanning electr
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Table 32.1 Acute 5-day data for corticosteroids delivered from the *BiodivYsio* Matrix LO stent

Stent	Lumen area (mm^2)	IEL area (mm^2)	EEL area (mm^2)	Neointimal hyperplasia (mm^2)	Area stenosis (%)
Control	7.94 ± 0.49	8.74 ± 0.44	10.44 ± 0.39	0.80 ± 0.16	9 ± 2
Dexamethasone	9.02 ± 0.49***	9.70 ± 0.49**	11.47 ± 0.69***	0.68 ± 0.12*	7 ± 1*
Methylprednisolone	8.34 ± 0.68	8.89 ± 0.73	10.26 ± 0.16	0.54 ± 0.16**	6 ± 2***

$n = 12$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to control.

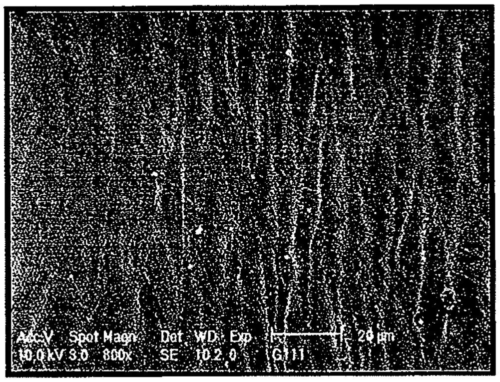

Figure 32.6

Scanning electron micrograph showing complete endothelialization of the drug-loaded stent.

reaction after angioplasty may have potent promoting effects on neointimal formation, reduction of these processes by delivery of a corticosteroid might be expected to have an effect on the early neointimal hyperplasia. Certainly, the number of macrophages in arteries healing after coronary intervention has been shown to correlate with the amount of tissue growth [24]. This was further supported by this study (see Table 32.1), with early neointimal hyperplasia and area stenosis of the dexamethasone and methyl prednisolone groups being significantly lower compared to those of the control group.

The inflammatory response at 4-weeks follow-up was still low, but higher than the 5-day time point with all stent groups being statistically equivalent. Endothelialization of the drug-loaded stents was identical to the control and hence unaffected by the presence of the drug (Figure 32.6).

The conclusion of the study was that local doses of the corticosteroids dexamethasone and methyl prednisolone delivered from Bio*divYsio* Matrix LO stents were safe for human clinical evaluation [25]. Furthermore, it was demonstrated that use of these drugs might be effective in decreasing the inflammatory response and potentially neointimal hyperplasia, without affecting the rate of endothelialization of the stent.

CLINCIAL EVALUATION OF STENT-MEDIATED DELIVERY OF DEXAMETHASONE—STRIDE

STudy of anti-Restenosis with the BIo*divYsio* Dexamethasone-Eluting stent (STRIDE). The aim of STRIDE was to evaluate the safety and efficacy of the Bio*divYsio* Matrix LO stent loaded with dexamethasone. The primary objective was to evaluate the proportion of patients having a clinical restenosis 6 months after receiving the dexamethasone-loaded stent. The secondary objectives were to evaluate the

safety and the 6-month quantitative coronary angiograph endpoints after receiving the dexamethasone-loaded stent.

STUDY DESIGN

This multicenter trial was performed at eight interventional cardiovascular centers in Belgium. Symptomatic patients with documented myocardial ischemia with de novo coronary lesions greater than 2.75 mm and less than 4.0 mm in diameter, with stenosis greater than 50%, and length less than 15 mm long were recruited.

PROCEDURE

All patients were premedicated with acetyl salicylic acid (ASA) (160 mg/d) orally. Oral ticlopidine 500 mg was given before PTCA. Standard balloon angioplasty was performed via the femoral approach. Heparin (100 U/kg), after insertion of the arterial sheath, was weight-adjusted and administered as needed to maintain an activated clotting time (ACT) of approximately 250–300 seconds. Intracoronary nitroglycerin 100–200 μg was administered immediately prior to baseline angiography, post-stent deployment, and after final post-dilatation angiography. Initial angiograms were performed in two orthogonal projections or, if not possible, in two different nonorthogonal views perpendicular to the investigated arterial segment. Under the same angiographic conditions, the same projections were repeated during the follow-up studies. After pre-dilatation, angiography was performed and evaluated. An appropriately sized Bio*divYsio* Matrix LO stent was selected and immersed in a solution of 15 mg/ml dexamethasone yielding approximately 0.5 $\mu g/mm^2$ of stent. The stent mounted on balloon was allowed to rest in the sterile solution for a minimum of 5 minutes and then was left to air dry in the sterile field for 5 minutes. After that time, the dexamethasone loaded Bio*divYsio* Matrix LO stent was deployed at the treatment site. In case of a suboptimal stent apposition, additional high pressure or upsized balloon inflations were performed. Procedural success was defined as a less than 10% diameter stenosis (DS) after stent implantation. After stent implantation, ASA was continued indefinitely and ticlopidine (250 mg/d) was prescribed for 28 days in all cases.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

Pre-procedural, post-PTCA, post-stent, and 6-month follow-up quantitative coronary angiographic measurements were performed offline using a computer-assisted automated arterial contour detection system (AWOS V 4.01, Siemens AG, Erlangen, Germany), which has been validated in vitro and in vivo. Each lesion was analyzed in two approximately orthogonal projections selected to maximally avoid superimposition and vessel foreshortening. The distal end of the guiding catheter was used for calibration in each analyzed projection. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion restenosis were defined as >50% DS at follow-up, located within the stent and target lesion, respectively. Reference and minimal luminal diameters (MLD), as well as the degree of percentage diameter stenosis before and after angioplasty, after stent implantation and at 6-month follow-up were studied. All measurements were assessed in both obtained views and averaged. Acute gain, late loss, and net gain were subsequently calculated. Acute gain was defined as the difference between the post- and pre-procedural MLD, while late loss and net gain were calculated by subtracting the MLD at control from the post-procedural and pre-procedural MLD, respectively [26].

CLINICAL FOLLOW-UP

All patients were asked to return to the investigative site or their primary cardiologist for a clinical visit 4 weeks post-procedure to monitor acute clinical events. All patients were contacted by telephone by the investigative site at 3 months + 1 week for a safety evaluation. All subjects were required to return to the investigative site for a repeat coronary angiography whether they were experiencing symptoms or not. If a patient had a positive exercise stress test at any time up to and including his required follow-up, a repeat angiogram was performed.

RESULTS

From January 16 to June 5, 2001, 71 patients from 8 study sites were included. Table 32.2 represents the baseline clinical characteristics of the study population. The mean age was 61.9 with a range from 42 to 82 years. Twenty-one percent were females. Sixty-three percent of the patients had hypercholesterolemia, 56% had hypertension, 42% had a previous MI, 46% had two or more than two vessel disease, 31% had lesion type B2 or C, 28% had unstable angina pectoris. Five patients were excluded from further analysis because of obvious protocol violations: one patient received a study stent to treat a no-reflow phenomenon after balloon dilatation, one patient had a documented AMI within 72 hours of the study procedure, one patient had a long tandem lesion (35 mm), treated by one study stent, overlapping with a long nonstudy stent, in one patient the study stent was implanted in a significantly diseased bifurcation of the Lad/ Diagonal, covering a diagonal >2 mm, Finally one patient with multiple vessel disease underwent a staged PTCA procedure.

Table 32.2 Baseline clinical characteristics

	n	%
Study population	71	
Female/male	12/56	21/79
Mean age	61.9 (range 42–82)	
Risk factors		
Family history CHD	24	34
Hypercholesterolemia	45	63
Hypertension	40	56
Peripheral vascular disease	5	7
Previous stroke	5	7
Previous MI	30	42
Previous PTCA	11	15
Smoking state		
Never smoked	16	23
Current smokers	24	34
Ex-smokers	25	35
Stable angina	29	42
Unstable angina	27	38
Silent ischemia	13	19

Values are mean ± SD or *n* (%).

ACUTE AND 30 DAYS CLINICAL FOLLOW-UP

All the stents were implanted successfully. One patient had recurrent angina pectoris, requiring a nontarget vessel revascularization at 15 days.

THREE-MONTH FOLLOW-UP

The 3-month follow-up was available for all the remaining patients. Two additional MACE occurred: one patient suffered an MI not related to the target vessel, and another patient had recurrence of symptoms due to progression of his coronary disease and was referred for CABG.

ANGIOGRAPHIC RESULTS

The angiographic characteristics of the stented coronary segments are presented in Table 32.3. Forty-six percent of the patients had at least two vessel disease. Thirty percent of stents

were placed in right coronary artery (RCA), 41% in the left anterior descending artery (LAD), and 20% in the circumflex coronary artery. Quantitative coronary analysis is summarized in Table 32.3. The mean lesion length was 9.99 mm with a range from 4 to 23.5 mm. The mean reference diameter at baseline was 2.95 ± 0.52 mm. MLD and diameter stenosis before the procedure were 1.03 ± 0.35 mm and 64.75 ± 11.81%, respectively. Six-month follow-up angiographic data have been collected and are awaiting analysis.

Table 32.3 Angiographic characteristics

	n	%
Disease state		
Single vessel disease	38	54
2 vessel disease	20	29
3 vessel disease	10	14
4 vessel disease	2	3
Vessels treated		
RCA	21	30
LAD	29	41
CX	14	20
First obtuse marginal	4	6
Ramus intermedius	2	3
Lesion classification[a]		
A	15	21
B1	34	48
B2	19	27
C	3	4
Lesion length	9.99 (range 4–23.5)	

Values are mean ± SD or *n* (%). CX, left circumflex artery.
[a]According to AHA/ACC classification.

SELECTED CASE STUDIES AT 6 MONTHS

Figure 32.7 shows a coronarogram of the left coronary artery showing a severe eccentric lesion of the mid-LAD. The lesion was pretreated with a 12/3.0 mm balloon and stented with a 16/3.5 mm study stent. At 6-month follow-up the treated vessel segment was still fully patent. Figure 32.8 shows a coronarogram of the left coronary artery showing a subtotal, eccentric lesion of the circumflex artery. The lesion was pretreated with a 12/2.5 mm balloon and stented with a 16/3.0 mm study stent. Six-month follow-up coronarogram revealed a moderate restenosis in the treated segment.

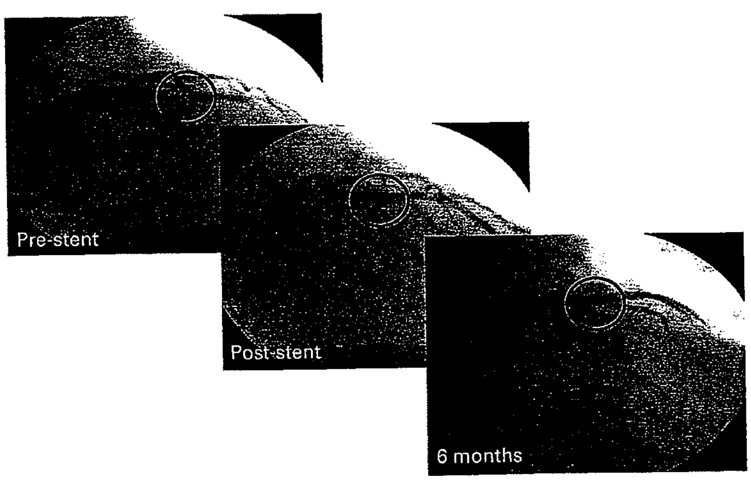

Figure 32.7
Case Study 1.

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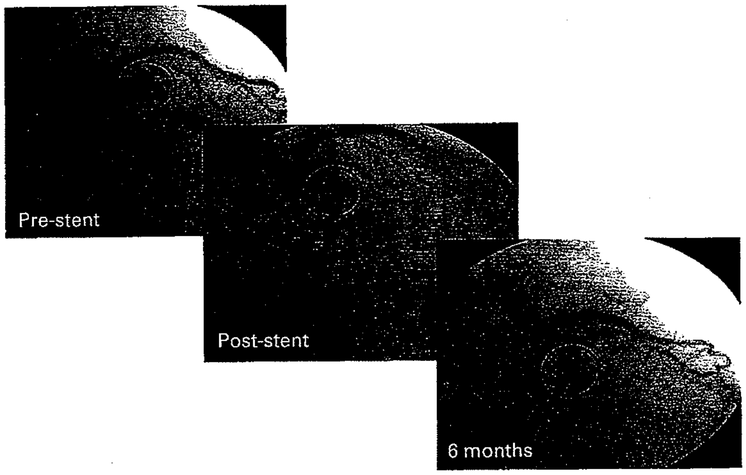

Figure 32.8
Case Study 2.

DISCUSSION AND CONCLUSIONS

Coronary stenting is still hampered by subacute in-stent early thrombosis and later in-stent restenosis. Although largely prevented by improved stent implantation and adjunctive treatment with thienopyridines (ticlopidine or clopidogrel), subacute thrombotic stent occlusion still occurs in less than 2% of cases and is often associated with a significant morbidity and mortality. The median time of thrombosis occurrence is 1 day with virtual elimination of events after day 2 after the stent implantation [27]. In patients undergoing intravascular brachytherapy an increased incidence of subacute and even late thrombotic stent occlusion have been reported. This was explained by the retarded regrowth of endothelial cells after intravascular brachytherapy. Also, drug-eluting stents are considered at risk for increased incidence of subacute and late stent thrombosis since the drug used to inhibit neointimal hyperplasia may also affect endothelial cell regrowth. In this pilot trial no increased incidence of subacute thrombosis was observed despite the lack of prolonged administration of ticlopidine. We await the 6-month angiographic data in order to assess whether the drug has had any effect on the extent of neointimal hyperplasia that has occurred in these patients.

Implantation of a dexamethasone loaded Biod*iv*Y*sio* Matrix LO stent to treat de novo coronary lesions is feasible and safe. Especially there was not an increased incidence of subacute nor late stent thrombosis notwithstanding the absence of prolonged antiaggregation treatment in this study. Clinical event rate and clinically driven revascularization need was low. This study however, was a pilot study that was neither blinded, nor randomized without a control group. It was performed in a small selected group of patients. Two further randomized studies are therefore planned to further investigate the effects of dexamethasone delivery on late loss (EMPEROR, Figure 32.9) and in patients with acute coronary syndromes (DESCEND, Figure 32.10).

EMPEROR

Evaluation of 9α-Fluoro-16-MethylPrednisolone Eluting stents on the Reduction Of Restenosis

Purpose	Comparative evaluation of lumen loss (MLD after stent placement—MLD at follow-up) 6 months after stent implantation between coronary lesions treated by 9α-F-16-Methylprednisolone (dexamethasone)-loaded Bio*divYsio* Matrix stents and Bio*divYsio* standard OC PC coated stents.
Trial phase	Phase II.
Structure	Multicenter, prospective, randomized clinical study.
Enrollment	420 subjects with proven coronary artery disease and angiographic follow-up in at least 330 patients..
Clinical sites	Approximately 20 sites in Germany, February 2002.
Principal investigators	PD Dr med. R Hoffmann, Universitätsklinikum, Aachen der RWTH, Germany.

Figure 32.9

Structure of the EMPEROR trial.

DESCEND

The Dexamethasone Eluting Stent in aCuteE coroNary synDromes.

Purpose	To evaluate the safety and efficacy of the Bio*divYsio* Matrix PC-coated stent loaded with dexamethasonein patients with acute coronary syndromes.
Trial phase	Phase II.
Structure	Multicenter, prospective, randomized clinical study.
Enrollment	160 patients with angiographic follow-up (80 randomized to receive a standard Bio*divYsio* stent and 80 to a Bio*divYsio* Matrix stent preloaded with dexamethasone).
Clinical sites	Approximately four sites in the United Kingdom, April 2002.
Principal investigators	Dr Peter M Schofield, Papworth Hospital, Cambridge, England.

Figure 32.10

Structure of the DESCEND trial.

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Persistent Inhibition of Neointimal Hyperplasia After Sirolimus-Eluting Stent Implantation

Long-Term (Up to 2 Years) Clinical, Angiographic, and Intravascular Ultrasound Follow-Up

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Background—Early results of sirolimus-eluting stent implantation showed a nearly complete abolition of neointimal hyperplasia. The question remains, however, whether the early promising results will still be evident at long-term follow-up. The objective of our study was to evaluate the efficiency of sirolimus-eluting stent implantation for up to 2 years of follow-up.

Methods and Results—Fifteen patients with de novo coronary artery disease were treated with 18-mm sirolimus-eluting Bx-Velocity stents (Cordis) loaded with 140 μg sirolimus/cm^2 metal surface area in a slow release formulation. Quantitative angiography (QCA) and intravascular ultrasound (IVUS) were performed according to standard protocol. Sirolimus-eluting stent implantation was successful in all 15 patients. During the in-hospital course, 1 patient died of cerebral hemorrhage after periprocedural administration of abciximab, and 1 patient underwent repeat stenting after 2 hours because of edge dissection that led to acute occlusion. Through 6 months and up to 2 years of follow-up, no additional events occurred. QCA analysis revealed no significant change in stent minimal lumen diameter or percent diameter stenosis, and 3-dimensional IVUS showed no significant deterioration in lumen volume. In 2 patients, additional stenting was performed because of significant lesion progression remote from the sirolimus-eluting stent.

Conclusion—Sirolimus-eluting stents showed persistent inhibition of neointimal hyperplasia for up to 2 years of follow-up. **(*Circulation.* 2002;106:1610-1613.)**

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs

Coronary stents provide a mechanical scaffolding that virtually eliminates recoil and remodeling, but they do not reduce neointimal growth. Sirolimus-eluting stents may provide a definitive solution for in-stent restenosis in the short term.[1,2,3] Histological follow-up in the porcine model, however has indicated that late neointimal hyperplasia can recur at 90 and 180 days (Andrew J. Carter, DO, unpublished data, 2001). Thus, there are sufficient concerns about delayed healing with consequent risks of late restenosis[4] and thrombosis,[5] late malapposition,[6] edge effect,[7] and, on the other hand, delayed restenosis,[8] to warrant additional late follow-up catheterization. The objective of this study was to determine angiographic, intravascular ultrasound (IVUS), and clinical outcome up to 2 years after implantation of sirolimus-eluting stents in de novo coronary lesions.

Methods

Patients and Stent Implantation

The patient population consisted of 15 patients who were included at our center between February and May of 2000 in the First in Man clinical trial on sirolimus-eluting stents (FIM). The methodology has been published previously.[3]

In brief, patients with short (<15 mm) de novo coronary lesions received a single 18-mm sirolimus-eluting Bx-Velocity stent (Cordis). All lesions were predilated before stent implantation. The sirolimus coating was a slow-release formulation (≈28-day drug release with 140 μg of sirolimus per cm^2 stent surface area). All patients received aspirin (325 mg/d, indefinitely) and clopidogrel (300 mg loading dose immediately and 75 mg/d for 8 weeks).

Angiographic and IVUS Analysis

Serial coronary angiography was performed at baseline, 6 months, and late follow-up (mean 20.3±2.4; range 18 to 24 months). Two

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TABLE 1. Baseline Characteristics

Male	10
Age, y	60.2±14.3 (35–80)
Unstable angina	9
Treated vessel	
LAD	6
CX	5
RCA	4
No. of diseased vessels	
1	13
2	2
Catheterization follow-up period, mo	20.3±2.4 (18–24)
Clinical follow-up period, mo	23.3±1.0 (22–25)

Values are n or mean±SD (range). n=15.

LAD indicates left anterior descending artery; CX, circumflex artery; and RCA, right coronary artery.

coronary segments were subjected to quantitative angiography (QCA), one in stent and one in lesion. The in-stent segment encompassed only the 18-mm segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion stenosis was defined as >50% diameter stenosis. QCA analysis was done by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

Stented vessel segments were examined with mechanical IVUS, using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program was used for automated 3-dimensional reconstruction of the stented segment from up to 200 cross-sectional images.[9]

Clinical Follow-Up

We assessed the clinical outcome during the hospital stay, at 6 months, and up to 2 years later. Major adverse cardiac events were defined as death, acute myocardial infarction, and repeat revascularization of the target lesion and/or vessel by coronary artery bypass graft or percutaneous coronary intervention.

Statistical Analysis

Quantitative data are presented as mean±SD. Multiple comparisons between postprocedural 6- and 20-month follow-up measurements were performed by ANOVA. Paired comparisons were performed by Student's t test.

Results

Six-month outcomes of the original 15 patients have been described earlier.[2] Baseline characteristics are shown in Table 1. In brief, between 6 months and up to 2 years after stent implantation, no additional clinical events occurred. Complete sets of postprocedural, 6-month, and late follow-up cardiac catheterizations were obtained in 10 of 14 surviving patients. Four asymptomatic patients refused to undergo a second diagnostic investigation for scientific purposes only.

TABLE 2. Major Adverse Cardiac Events

	6 Months	6 to 24 Months	Up to 24 Months
Death	1†	0	1
MI*	1	0	1
TLR*	1	0	1
TVR	0	2	2
CABG	0	0	0

n=15.

MI indicates myocardial infarction; TLR, target-lesion revascularization; TVR, target-vessel revascularization; and CABG, coronary artery bypass graft.

*The same patient (periprocedural MI).

†Due to cerebral hemorrhage in hospital.

At 18 months after the procedure, 1 patient demonstrated a significant stenosis (60% diameter stenosis; fractional flow reserve 0.65) located distally to the sirolimus stent (8 mm from distal edge by quantitative IVUS) that was treated by direct stenting. Another patient presented with effort angina 22 months after the index procedure and underwent stenting because of progression of a preexisting atherosclerotic lesion 12 mm from the distal edge of the sirolimus stent (minimal lumen area by IVUS 3.5 mm^2 after the procedure and 3.0 mm^2 at 22-month follow-up). Volumetric IVUS measurements showed no neointimal hyperplasia (NIH) in the stented segment. Lumen volume of both 5-mm proximal and distal edges of the sirolimus stent revealed virtually no changes when comparing postprocedural, 6-month, and 22-month follow-up measurements.

At almost 2 years of follow-up, 1 death (noncardiac) and 1 target-lesion revascularization occurred, both of which were in the early in-hospital period (Table 2).

Quantitative Coronary Angiography and IVUS Analysis

Quantitative coronary angiography data are shown in Table 3. Twenty-month in-stent minimum lumen diameter (2.74±0.41 mm) and percent DS (3±13%) remained unchanged compared with 6-month follow-up data

TABLE 3. Quantitative Coronary Angiography Analysis

	Before Procedure	After Procedure		6-Month Follow-Up		20-Month Follow-Up	
		In Lesion	In Stent	In Lesion	In Stent	In Lesion	In Stent
RD, mm	2.97±0.51	3.01±0.43		3.02±0.38		2.85±0.40	
MLD, mm	0.81±0.24	2.58±0.43	2.90±0.33	2.32±0.37	2.69±0.30	2.50±0.51	2.74±0.41
Stenosis, %	72±8	14±10	1.5±7	23±7	11±8	12±15	3±13
Late loss, mm				0.25±0.31	0.25±0.28	0.08±0.46*	0.20±0.24*
Late loss index				0.13±0.20	0.12±0.11	0.02±0.30*	0.10±0.13*

Values are mean±SD. n=10.

RD indicates reference diameter; MLD, minimal lumen diameter.

*P=NS (6-month vs 20-month follow-up). P=NS between groups (after procedure, 6-month, and 20-month follow-up). Comparison by ANOVA.

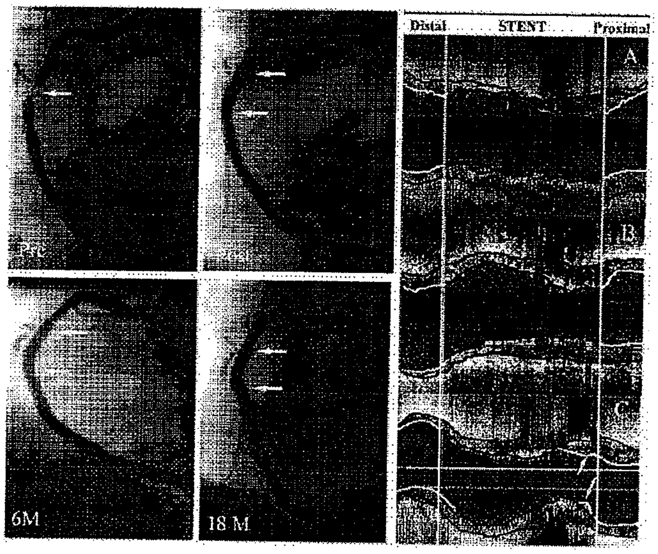


Figure 1. A 38-year-old male with unstable angina and mid-right coronary artery lesion (arrow) treated with sirolimus-eluting Bx-velocity stent. No lumen deterioration was observed at 6- and 18-month follow-up (6M and 18M). Longitudinal IVUS reconstructions demonstrate absence of NIH at 6-month follow-up (B), with minimal NIH (C, arrows) at 18 months compared with after the procedure (A).

(2.69±0.30 mm and 11±8%, respectively; P=NS). Representative sequences of angiograms from a single patient are shown in Figure 1.

IVUS analysis demonstrated persistent inhibition of NIH at long-term follow-up (Table 4). FIM study data from Sao Paulo cohort are also shown in Table 4. Between the 6- and 20-month follow-ups, a small change in NIH (1.4±1.6 mm^3 and 5.9±5.3 mm^3, respectively) and in percent volume obstruction of the stent (1.1±1.2% and 4.4±3.1%, respectively) was observed. Only 1 patient reached 10% NIH of stent volume as shown by IVUS, which corresponded with an actual luminal loss of 0.29 mm at the 18-month follow-up (Figure 1). In addition, no significant change in lumen or vessel volume was observed in either proximal or distal edges of the stent (Figure 2). No late stent malapposition was detected.

Discussion

First clinical applications of sirolimus-eluting stents in de novo lesions were shown to be safe and feasible in preventing NIH at 6 months and 1 year, with a complete abolition of restenosis.[1–3] Such findings have provoked considerable interest but have also raised concerns about the long-term follow-up[10,11]

TABLE 4. Volumetric IVUS Measurements

	Rotterdam (n=10)		Sao Paulo (n=14)*	
Follow-up period, mo	6	20	4	12
Stent volume	133±31	132±29	138±21	127±30
Lumen volume	132±31	126±28	137±22	124±30
NIH volume	1.4±1.6	5.9±5.3†	0.3±0.9	2.5±3.4
% Volume obstruction	1.1±1.2	4.4±3.1†	0.3±0.8	2.2±3.4

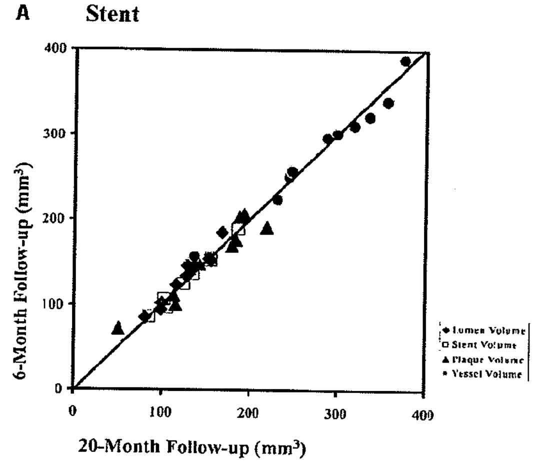
*Data from Sao Paulo[3] (slow-release formulation stent group).
†P<0.05, 6-month vs 20-month follow-up.

In the present study, NIH assessed by IVUS at both 6 and 20 months was not substantially different from the 12-month follow-up data presented by Sousa et al[3] (Table 3). In addition, the percent volume obstruction of the stent detected by volumetric IVUS in our study (4.4%) at 20-month follow-up is importantly less than those observed at 6-month follow-up in other trials (36% and 25%) using uncoated stents.[12,13] Similarly, in-stent late loss and late loss index (LLI; 0.20 mm and 0.10, respectively) at a 20-month follow-up is markedly lower than with bare metal stents, in which late loss averages were 1.04 to 0.61 mm (LLI 0.59 to 0.39) at a 6-month[12,13] and 0.46 mm (LLI 0.30) at a 36-month follow-up.[14] Therefore, our findings provide considerable reassurance with regard to persistent inhibition of late restenosis or rebound hyperplasia, such as was previously observed with radioactive stents.[8]

In fact, minimal hyperplasia in humans up to 2 years after the procedure constitutes the first evidence that behavior in humans is at variance with the porcine model, where 90-day data actually demonstrate the recurrence of considerable NIH (Andrew J. Carter, unpublished data). For the first time in interventional cardiology, a new antirestenosis therapy performs better in humans than in the animal models.

Concern about potential late complications, such as late occlusion, thrombosis, late malapposition, aneurysm, and edge restenosis as reported in patients treated with brachytherapy,[13] has not been observed in our patient population during up to 2 years of follow-up.

It has to be emphasized that short-term (8-week) antiplatelet therapy as used here and in the RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent (RAVEL)[15] provides adequate protection against subacute and late thrombotic occlusion. Nonetheless, generalization of these findings to treatment of long and complex lesions, total chronic occlusion, left main stem, etc, needs to be specifically evaluated in clinical trials.



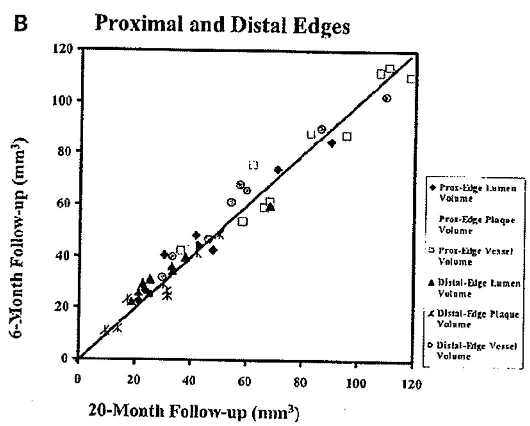


Figure 2. Changes in vessel, plaque, and lumen volume at the sirolimus-eluting stent (A) and peri-stent margins (5-mm proximal and 5-mm distal edges of the stent) (B). Individual data are presented in relation to the line of identity. *P*=NS for 6-month versus 20-month follow-up

The need for late target-vessel revascularization in 2 patients in lesions remote from the sirolimus stent again emphasizes the indolent nature of atherosclerosis in some patients. Although this study confirms that sirolimus-eluting stents constitute a major advance in restenosis prevention, the problem of atherosclerosis itself remains a considerable challenge.

Limitations

This is a small observational study and the results need to be confirmed by long-term follow-up in larger patient series. Lack of complete QCA and IVUS follow-up was unfortunate but was not prespecified in the study protocol. The virtual absence of NIH in the 10 patients studied at 20 months renders the data quite compelling because the remaining 4 patients were completely asymptomatic.

Conclusion

Sirolimus-eluting Bx-Velocity stents demonstrated persistent inhibition of neointimal hyperplasia and absence of restenosis in single de novo coronary lesions for up to 2 years of follow-up.

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Angiotensin-Converting Enzyme Inhibition With Fosinopril Sodium in the Prevention of Restenosis After Coronary Angioplasty

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Background Several angiotensin-converting enzyme inhibitors have antiproliferative effects in a rat model after carotid artery balloon injury.

Methods and Results We conducted a randomized, double-blind, placebo-controlled trial to assess the effect of fosinopril, a novel angiotensin-converting enzyme inhibitor, in restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received fosinopril or matched placebo 10 mg at least 18 hours before PTCA, 20 mg at least 4 hours before PTCA, and 40 mg daily for 6 months. In addition, all patients received aspirin. Coronary angiograms before PTCA and immediately after PTCA as well as at 6-month follow-up were quantitatively analyzed. A total of 509 patients were recruited. The final per-protocol population consisted of 153 fosinopril-treated and 151 placebo-treated patients. Restenosis rates according to the National Heart, Lung, and Blood Institute criterion 4 (loss of ≥50% of the initial gain [primary end point]) were 45.7% and 40.7% in the fosinopril and control groups, respectively (not significant). The respective mean differences in minimal coronary luminal diameter between post-PTCA and follow-up angiograms were -0.59 ± 0.71 mm and -0.51 ± 0.67 mm (not significant). Clinical events during the 6-month follow-up period, analyzed on an on-treatment basis, were ranked according to the most serious event. The respective numbers in the fosinopril and the control groups were for death, 0 and 0; myocardial infarction, 0 and 0; coronary artery bypass graft surgery, 1 and 3; repeat PTCA, 35 and 31; recurrent signs of ischemia necessitating early repeat coronary angiography and managed medically, 6 and 7; and none of the above, 111 and 106. All these differences were insignificant.

Conclusions Administration of fosinopril in a dose of 40 mg daily during 6 months after PTCA does not prevent restenosis and has no effect on overall clinical outcome. (*Circulation*. 1994;89:385-392.)

Key Words • angioplasty • fosinopril

Restenosis remains the major factor limiting the long-term success of percutaneous transluminal coronary angioplasty (PTCA), and to date, no treatment regimen has shown indisputable efficacy in preventing this phenomenon.[1-11] Previous experimental work demonstrated that smooth muscle cell proliferation plays an important role in the restenosis process. Locally produced angiotensin II might act as a comitogen through binding to specific angiotensin II receptors, present in high numbers on medial smooth muscle cells.[12-15] In addition, in normotensive rats with balloon-induced carotid artery injury, pretreatment with high doses of angiotensin-converting enzyme (ACE) inhibitors decreased the neointimal proliferation by 80%, but this beneficial effect could not be reproduced in a similar pig model.[16-19]

Fosinopril sodium is an ester prodrug of a new inhibitor of ACE. Fosinopril contains a phosphinic acid group instead of a sulfhydryl group and undergoes metabolic hydrolysis, primarily by gut and liver, to the active diacid fosinoprilat, which is extensively protein bound. In healthy subjects, absorption of fosinopril averages 36%, and the bioavailability of fosinoprilat averages 29%. The terminal elimination half-life of fosinoprilat after intravenous administration is 12.4 hours. In healthy subjects, excretion is about equally divided between biliary and renal routes.

The present single-center trial was undertaken to test the influence of a clinical dose of this novel inhibitor of ACE on the occurrence of angiographically documented restenosis and on clinical events during a 6-month follow-up period after successful PTCA.

Methods

Study Population

All patients scheduled for elective PTCA in our center were considered for inclusion. The study protocol was approved by the Ethical Committee of the University Hospital, Leuven, Belgium, and oral witnessed informed consent was obtained before randomization.

Exclusion criteria consisted of age >80 years, women of childbearing potential, inability to withdraw calcium channel blockers and nitrates before PTCA, PTCA for restenosis, PTCA for total occlusion, PTCA of a saphenous vein or internal mammary artery graft, ACE inhibitor treatment within 1 month before entry, systolic blood pressure <100 mm Hg or diastolic pressure >95 mm Hg at entry, a history of cerebrovascular accidents, significant cardiac valvular disease, significant renal or hepatic disease, acute myocardial infarction within 2 weeks before entry, leukopenia or neutropenia, a history of collagen vascular disease, current therapy with

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TABLE 1. Reasons for Exclusion

	N	%
Total No. of patients screened	1156	100
No. of patients recruited	509	44.0
Reason for exclusion		
PTCA for restenosis	180	15.6
Not hospitalized on day before PTCA	90	7.8
Decision for PTCA to be made during angiography	84	7.3
Recent myocardial infarction	43	3.7
ACEI treatment	41	3.5
Significant concomitant disease	41	3.5
Atherectomy, laser, or stent implantation planned	27	2.3
No informed consent given	25	2.2
History of CVA	22	1.9
Logistic reasons	19	1.6
Malignancy	15	1.3
Inability to withdraw calcium channel blockers and nitrates	12	1.0
PTCA of a bypass graft	12	1.0
Other reasons* (<1% each)	58	5.0

PTCA indicates percutaneous transluminal coronary angioplasty; ACEI, angiotensin-converting enzyme inhibitor; and CVA, cerebrovascular accident.

*Inclusion in another trial; age >80 years; aortic stenosis; familial homozygous hypercholesterolemia; intolerance for ACE inhibitors; depression; allergy to iodinated agents; PTCA for total occlusion; systolic blood pressure <100 mm Hg.

cytotoxic or immunosuppressant drugs, and a history of drug or alcohol abuse (Table 1).

Of the 1156 patients screened between April 1991 and January 1992, 509 patients (44%) were enrolled.

After randomization, patients were discontinued early (ie, before hospital discharge) from study medication when symptomatic or significant hypotension (systolic blood pressure <85 mm Hg) developed as well as for a number of anatomic and procedural reasons. First, medication was discontinued in patients who did not comply with the definition of successful PTCA, ie, an initial measured percent diameter stenosis of >50% reduced by at least 20% to a residual stenosis of <50%. Second, patients who had developed a total occlusion between the diagnostic procedure and the PTCA were also discontinued. Finally, treatment was discontinued when stent implantation or urgent bypass surgery was indicated or when other adverse procedural events occurred.

Study Medication

After randomization, trial medication was started at least 18 hours before the PTCA procedure. The first dose consisted of 10 mg of fosinopril or matching placebo. At least 4 hours before PTCA, 20 mg was administered, and on the day after PTCA the dose was increased to 40 mg, which was continued until follow-up angiography. Concomitant therapy with calcium channel blockers was discontinued on the day before PTCA. During the hospital stay, blood pressure was monitored hourly for 3 hours after every drug administration. If systolic blood pressure fell below 85 mm Hg or if symptomatic hypotension occurred, treatment was discontinued. If systolic blood pressure was <100 mm Hg but >85 mm Hg, the 20-mg dose was maintained during the follow-up period.

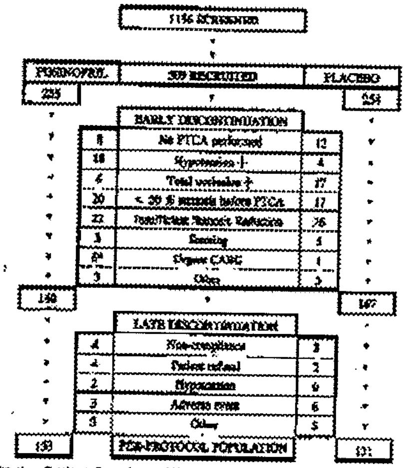

FIG 1. Patient flowchart. PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery. *Two deaths. †P=.005; ‡P=.03. All other differences between treatment groups are insignificant.

Follow-up Evaluation

Patients visited their referring cardiologist after 2 and 4 months for interview, cardiac examination, electrocardiography, laboratory tests, and pill count. The same procedures were repeated at 6 months, when the follow-up angiography was performed in our center. However, in patients with early recurrence of symptoms or evidence of silent ischemia, coronary angiography was carried out earlier. During follow-up, patients were considered treatment compliant only if at least 80% of the medication was taken, as judged from the pill counts at 2, 4, and 6 months, and only these patients were used for the final evaluation of the drug effect.

PTCA Procedure and Quantitative Angiographic Analysis

PTCA was performed according to standard procedures, but choices of vascular access, balloon type and size, inflation duration, and inflation pressure were left to the discretion of the operator. An intravenous bolus of heparin 10 000 IU was administered at the beginning of the procedure, followed by an intravenous infusion at a rate of 1000 IU/h, which was continued for 24 hours. If the procedure lasted for more than 1 hour, an additional bolus of heparin 5000 IU was given. Coronary arteriograms were obtained with a real-time digital image acquisition and processing system (Polytron 1000, Siemens AG, Erlangen, Germany). Images were acquired at 25 frames per second in a 512×512 matrix, with a pixel depth of 10 bits, equivalent to 1024 gray steps per pixel. Thereafter, images were either analyzed on-line or stored on hard disk or streamer tape for later analysis. Each lesion was analyzed in two approximately orthogonal projections, selected to maximally avoid superimposition and vessel foreshortening. Identical projections and source-patient-image intensifier distances were used for the pre- and post-PTCA angiograms as well as for the follow-up angiogram in each patient. Before contrast injection, both before and after PTCA, as well as at follow-up, 200 μg intracoronary nitroglycerin was given to induce maximal vasodilation. All measurements were performed on se-

Table 2. Baseline Characteristics of the Per-Protocol Population

	Fosinopril Patients (N=153)	Control Patients (N=151)
Sex, M/F	118/35	118/33
Age, y	59.0±8.4	59.3±8.4
Weight, kg	73.6±10.6	73.6±10.3
Height, cm	168.2±8.2	168.0±8.2
Heart rate, bpm	66.7±10.6	65.4±10.1
Blood pressure, mm Hg		
Systolic	135.5±19.6	136.1±17.4
Diastolic	79.6±9.6	79.7±9.4
LDL cholesterol, mg/dL	158.7±47.1	161.1±43.4
Angina class (CCS), n (%)		
Asymptomatic	12 (7.8)	9 (6.0)
Class I	26 (17.0)	18 (11.9)
Class II	38 (24.8)	30 (19.9)
Class III	41 (26.8)	50 (33.1)
Class IV	36 (23.5)	44 (29.1)
Medication, n (%)		
Nitrates	67 (43.8)	70 (46.4)
Calcium antagonists	57 (37.3)	58 (38.4)
β-Blocking agents	80 (52.3)	91 (60.3)

bpm indicates beats per minute; LDL, low-density lipoprotein; and CCS, Canadian Cardiovascular Society functional class. Data are expressed as mean±SD. All differences between the two treatment groups are insignificant.

Table 3. Anatomic Baseline Characteristics of the Per-Protocol Lesions

	Fosinopril Group (175 Lesions)	Control Group (172 Lesions)
Vessel dilated, n (%)		
RCA	59 (33.7)	68 (39.5)
LAD	65 (37.1)	62 (36.1)
LCx	51 (29.2)	42 (24.4)
Number of sites dilated, n (%)		
One	133 (86.9)	130 (86.1)
Two	18 (11.8)	21 (13.9)
Three	2 (1.3)	0 (0.0)
Lesion type, n (%)		
Tandemlike	29 (16.6)	34 (19.8)
Length >2×vessel diameter	72 (41.1)	89 (51.7)
Lesion in >45° bend*	52 (29.7)	72 (41.9)
Thrombotic	11 (6.3)	11 (6.4)
Calcified	33 (18.9)	34 (19.8)
Eccentric	129 (73.7)	129 (75.0)
Lesion complexity score,† n (%)		
Type A	29 (16.6)	25 (14.5)
Type B1	79 (45.1)	64 (37.2)
Type B2	56 (32.0)	72 (41.9)
Type C	11 (6.3)	11 (6.4)

RCA indicates right coronary artery; LAD, left anterior descending artery; and LCx, left circumflex artery.

*P=.02; all other differences between the two treatment groups are insignificant.

†According to the American College of Cardiology/American Heart Association Task Force classification system.[28,29]

lected end-diastolic frames, with lesion and adjacent "normal" segment being equally opacified.

Quantitative coronary analysis was performed with a commercially available, semiautomated system (Polytron 1000) that was earlier validated in vitro and in vivo.[30,31] Image calibration was performed with an 8-mm-thick metal cylindrical bar. In every patient, at the end of the procedure, the bar was filmed in each projection at a fixed distance of 12 cm from the image intensifier with source-intensifier distances identical to those for the coronary angiogram. This metal bar was preferred to the guiding catheter as a calibration device because it is known that differences in determining the absolute dimensions of coronary lesions can result from different catheters being used as scaling devices.[32] For each lesion, measurements were repeated three times by the same operator on the same selected digital images. A second observer repeated the same procedures on the same preselected frames. For calculation, the mean values of all six measurements obtained in each of both projections by both operators were used.

End Points

The primary end point of this study was the incidence of angiographically documented restenosis at follow-up as defined by National Heart, Lung, and Blood Institute (NHLBI) criterion 4, ie, loss of ≥50% of the initial gain after PTCA. In multilesion PTCA, the lesion with the largest increase in minimal luminal diameter (MLD) after the procedure was considered the index lesion for follow-up. Secondary end points were the within-patient change in MLD, defined as the follow-up value minus the post-PTCA value as well as clinical cardiovascular events (death, recurrence of angina, acute myocardial infarction, need for repeat PTCA, or coronary artery bypass graft surgery).

Statistical Methods and Analysis

At the time the original protocol was designed, a restenosis rate of 30% according to NHBLI criterion 4 within the 6 months subsequent to initially successful PTCA was expected. To detect a postulated one-third reduction in the incidence of restenosis due to fosinopril, 313 patients per group having the required three angiograms (pre- and post-PTCA and at follow-up) were necessary to achieve a power of 0.80, allowing a type I error of 0.05 (two-tailed). Assuming that of all randomized patients, 2% would not complete the PTCA procedure, that 10% would experience unsuccessful PTCA, that follow-up angiograms would be unavailable in 14% of those successfully treated, and thus that identification of restenosis would be precluded in 23.4% of randomized patients, the sample size was fixed at 410 patients per group (313/0.766=410) to maintain study power for evaluating the primary end point.

At the time 409 patients were randomized, however, the sponsor decided to stop the study. This decision was based on the report that another ACE inhibitor failed to alter the restenosis rate in the MERCATOR trial[23] in conjunction with the results of an interim analysis of our first 100 patients who completed the study, indicating no trends of the effect of fosinopril on clinical or angiographic restenosis rate. However, the overall incidence of angiographically defined restenosis

according to NHLBI criterion 4 (47%) was much higher than the projected rate of 30%, thereby increasing the power of the study to detect a treatment effect.

Since the change in MLD after PTCA has been shown to follow a near-gaussian distribution,[24] parametric tests were used. The treatment effect was defined as the difference in mean change in MLD as well as in percent stenosis between the two treatment groups.

Angiographic and clinical outcome was evaluated for all randomized patients who after PTCA still complied with all inclusion criteria. At the time of follow-up, each patient was assigned to the most serious applicable event. For comparison of the clinical outcome between the two treatment groups, standard nonparametric statistical methods were used.

Results

Patients

During the enrollment period, 1156 patients were screened, of whom 509 were randomized. Trial medication was discontinued during the hospital stay in a total of 173 patients. Hypotension, defined as above, occurred in 22 patients. All other early discontinuations were for anatomic or procedure-related reasons (Fig 1). In 20 patients, after the pre-PTCA control angiogram, the lesion was no longer considered an indication for PTCA. In 23 patients, a total occlusion had developed within the interval between the diagnostic and the therapeutic procedures. Before PTCA, the degree of stenosis appeared to be <50% in 37 patients. An unsatisfactory PTCA result, ie, inadequate stenosis reduction as defined above, was encountered in 48 patients. Bail-out stenting and emergency bypass graft surgery were performed in 8 and 7 patients, respectively. Finally, 8 additional patients were discontinued early for various reasons: technical problems with the angiographic measurements and acute vessel closure in 3 patients each and a major dissection resulting in a limited myocardial infarction and protocol violation in 1 patient each. The subdivision of these early discontinuations by treatment group is depicted in Fig 1. Hypotension was more frequent after fosinopril ($P=.005$), and total occlusions were more frequent after placebo ($P=.03$), all other differences being insignificant.

As a result of these early discontinuations, a total of 336 study patients were discharged from the hospital: 169 fosinopril-treated and 167 placebo-treated. Of these patients, follow-up angiography was not obtained in a total of 32 patients: 7 patients were noncompliant in taking their study medication; in 2 patients late symptomatic hypotension developed; and in 9 patients treatment had to be interrupted because of other adverse events (unstable angina and rash or pruritus in 2 patients each; excessive perspiration, retroperitoneal bleeding, gastric ulcer, acute myocardial infarction, and asystole with successful resuscitation in 1 patient each). Follow-up angiography was refused by 6 additional patients. Finally, 8 patients were excluded for various reasons: 3 patients were lost to follow-up; in 4 patients, quantitative coronary angiography was not available for technical reasons; and 1 patient violated the protocol. The subdivision of these late dropouts between the two treatment groups is also depicted in Fig 1, all differences being insignificant.

Thus, the final per-protocol population consisted of 304 patients, 153 treated with fosinopril and 151 treated with placebo. In the fosinopril group, a total of 138 patients were discharged from the hospital on the full 40-mg dose and 15 on the reduced 20-mg dose. In the control group, the respective numbers were 140 and 11. The clinical and angiographic baseline characteristics of this per-protocol population are given in Tables 2 and 3[25,26]; all differences between both treatment groups were insignificant, except for a significantly greater number of patients in the control group with a lesion in a >45° bend.

Effects of Fosinopril on Angiographic End Points

Table 4 summarizes the quantitative angiographic findings of the per-protocol population. PTCA increased the MLD by 1.24±0.35 mm and by 1.16±0.38 mm in the fosinopril and control groups, respectively (not significant [NS]). The corresponding decreases in percent diameter stenosis were 42.8±13.9% and 40.2±14.8% (NS). At follow-up, the loss in MLD compared with the result immediately after PTCA was −0.59±0.72 mm in the active treatment group and −0.51±0.67 mm in the control group, resulting in a treatment effect of −0.0795 mm (95% confidence interval of −0.236 to 0.0771 mm). Expressed as percent diameter stenosis, the loss at follow-up was 20.5±23.0% in the patients treated with fosinopril and 17.5±23.6% in the control group (NS).

Fig 2 represents a cumulative distribution curve of MLD before PTCA, after PTCA, and at follow-up in both treatment groups; at each of these three stages, both curves are virtually superimposed. Fig 3 depicts the cumulative distribution of the change in MLD from before PTCA to follow-up, demonstrating that the net gain at the end of the follow-up period was comparable in the two treatment groups. Finally, Table 5 summarizes the restenosis rates in the per-protocol population per lesion according to seven currently used restenosis criteria; irrespective of the criterion used, the difference in restenosis rate between the two treatment groups was insignificant.

Effects of Fosinopril on Clinical End Points

During follow-up, dose reduction was indicated in 10 fosinopril-treated patients, invariably because of symptomatic hypotension. In the control population, dose reduction of study medication was not observed. The clinical status of the patients at the end of the follow-up period is given in Table 6. No patient of the per-protocol population died or suffered a myocardial infarction. In the fosinopril- and the placebo-treated groups, 77.1% and 70.2% of the patients, respectively, remained asymptomatic, but 9.8% and 10.6% of the respective patients were readmitted with angina at rest (NS). Early repeat PTCA was indicated in 19 fosinopril-treated and 18 control patients (of whom 2 patients had PTCA for another lesion), but elective bypass surgery was preferred in an additional 1 and 3 patients, respectively (NS). The various clinical indications for these interventions are listed in Table 6. At the time of the scheduled 6-month hospital admission, PTCA was performed in conjunction with the diagnostic procedure in 16 fosinopril- and 17 placebo-treated patients (NS). The indication was either angina pectoris, silent ischemia, or strictly angiographic, when a critical restenosis jeopardized a large area of viable myocardium.

TABLE 4. Quantitative Angiographic Analysis of the Per-Protocol Patients

	Fosinopril Group (N=153)	Control Group (N=151)
Obstruction diameter, mm		
Before PTCA	0.90±0.31	0.92±0.32
After PTCA	2.14±0.37	2.08±0.40
Follow-up	1.54±0.70	1.57±0.66
Reference diameter, mm		
Before PTCA	2.80±0.60	2.92±0.50
After PTCA	2.87±0.59	2.97±0.60
Follow-up	2.87±0.56	2.88±0.57
Difference in obstruction diameter, mm		
After vs before PTCA	1.24±0.35	1.16±0.38
Follow-up vs after PTCA*	−0.60±0.71	−0.51±0.67
Diameter stenosis, %		
Before PTCA	69.2±11.0	68.8±12.1
After PTCA	26.4±11.9	28.6±11.0
Follow-up	46.9±23.6	46.1±23.1
Difference in diameter stenosis, %		
After vs before PTCA	−42.8±13.9	−40.2±14.9
Follow-up vs after PTCA	20.5±23.0	17.5±23.6

PTCA indicates percutaneous transluminal coronary angioplasty. Data are expressed as mean±SD. All differences between both treatment groups are insignificant.
*SE difference=0.0796; Difference=−0.0795; 95% confidence interval=−0.236 to 0.0771.

Clinical events during the 6-month follow-up period were also analyzed on an intention-to-treat basis and ranked according to the most serious event. The respective numbers in the fosinopril and the control groups were, for death, 2 and 0; myocardial infarction, 4 and 3; coronary artery bypass graft surgery, 15 and 10; repeat PTCA, 31 and 53; recurrent signs of ischemia necessitating early repeat coronary angiography and managed medically, 11 and 11; and none of the above, 172 and 177. All these differences were insignificant.

Discussion

The present data show that ACE inhibition with fosinopril fails to prevent angiographic restenosis after successful PTCA of primary coronary arterial stenoses. Furthermore, the incidence of late clinical cardiovascular events was similar during fosinopril and placebo treatment. These findings are in complete agreement with the results of the MERCATOR trial,[23] in which no influence of the ACE inhibitor cilazapril on angiographic restenosis and on clinical end points could be demonstrated.

The trial design of the present study, however, differed in some aspects from the design of the above-mentioned study. In the present trial, study medication was initiated the day before the PTCA procedure, whereas in MERCATOR it was not started until the evening after successful PTCA. We preferred the for-

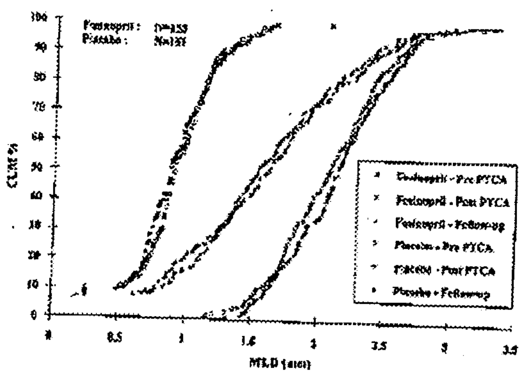

FIG 2. Cumulative distribution curve (CUM%, cumulative percentage of patients) of the minimal lumen diameter (MLD) before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at 6-month follow-up in both treatment groups.

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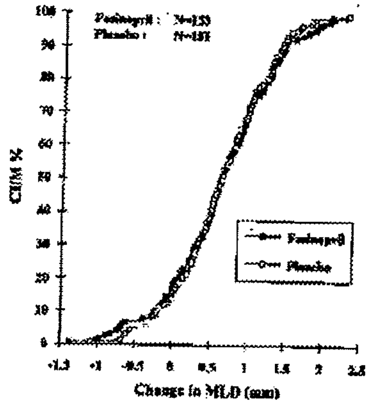

FIG 3. Cumulative distribution curve (CUM%, cumulative percentage of patients) of the change in minimal lumen diameter (MLD) from before percutaneous transluminal coronary angioplasty (PTCA) to follow-up in both treatment groups.

mer approach because experimental studies had demonstrated maximal inhibition of neointimal proliferation after pretreatment with ACE inhibitors. This earlier drug administration, however, did not beneficially affect the end points of the study. As a consequence of this strategy, a substantial number of patients had to be discontinued early for procedural reasons. Patients were discontinued when no PTCA was performed, when a total occlusion had developed during the interval between the diagnostic procedure and PTCA, when the immediate pre-PTCA stenosis was measured as <50%, or when the procedural gain was insufficient. In a small number of patients, trial medication was discontinued because of stent implantation or emergency coronary surgery after a complicated PTCA procedure. The total number of early discontinuations was very similar in both treatment groups, but hypotension was a more frequent cause in fosinopril-treated patients, and a total vessel occlusion was more frequently observed in the control group. We do not believe, however, that this sequence of events introduced any bias regarding the prevention of late restenosis. We preferred the present way of handling the data to a "true" intention-to-treat analysis because the high number of early discontinuations for procedural and anatomic reasons, although comparable in both treatment groups, can only be expected to prohibit meaningful interpretation of the data. Furthermore, it seems futile to compare angiographic data obtained in noncompliant patients.

Selection of doses was based on a review of data obtained in hypertensive patients and consistent with the objective of efficacy combined with acceptable safety. The most consistently effective dose of fosinopril in previous hypertension studies was 20 mg administered once daily. In normal subjects, ACE inhibition at 12 hours was 100% for both 20 and 40 mg of fosinopril. At 24 hours, 40 mg produced 98% inhibition, and 20 mg produced 80% inhibition. Within this range, no dose-related adverse effects could be identified. On the basis of these data, a daily dose of 40 mg of fosinopril was chosen for this study, but in spite of these considerations, 18 of 247 fosinopril-treated patients versus only 4 of the 242 control patients had to be discontinued early because of hypotension. In addition, in 15 of the 153 fosinopril-treated patients, dose titration had to be stopped at 20 mg, and in another 10 patients, the 40-mg dose had to be reduced to 20 mg because of hypotension.

In the present study, compared with MERCATOR, more severe lesions located in larger vessels were dilated: the respective pre-PTCA MLD values were 0.91 and 1.01 mm and the respective reference vessel diameters 2.91 and 2.63 mm, leading to calculated percent diameter stenoses of 69.0% in the present study versus 60.8% in the MERCATOR trial. In addition, our procedural gain of 1.30 mm was much higher than the 0.77 mm obtained in MERCATOR, so that, despite the more severe initial lesion, the residual stenosis was less severe (mean, 27.5% versus 32.9%). Subsequently, however, this larger procedural gain was offset to some extent by a greater loss in MLD (−0.55 mm versus −0.28 mm), leading to negligible differences between the two studies in the final 6-month follow-up result. Indeed, at this time, the MLDs obtained in the two studies were almost identical. In terms of percent stenosis, however, the values in the present study were slightly higher (46.5% versus 43.9%) because of a larger mean vessel diameter. The larger loss in MLD in the present study can best be explained by the larger initial gain itself, a relation recently reported by Serruys and

TABLE 5. Restenosis Rates per Lesion According to Frequently Used Definitions

Restenosis Criteria	Fosinopril Group (N=175)	Control Group (N=172)
>30% increase in % diameter stenosis at follow-up (NHLBI 1), n (%)	46 (26.3)	40 (23.0)
>70% diameter stenosis at follow-up, n (%)	22 (12.6)	22 (12.8)
Return to within 10% of the pre-PTCA diameter stenosis (NHLBI 3), n (%)	46 (26.3)	47 (27.3)
Loss of >50% of the initial gain after PTCA (NHLBI 4), n (%)	80 (45.7)	70 (40.7)
% Diameter stenosis at follow-up >50%, n (%)	69 (39.4)	64 (37.2)
Loss of ≥0.72 mm in MLD from post-PTCA to follow-up, n (%)	58 (33.1)	64 (37.2)
Loss of ≥0.38 mm in MLD from post-PTCA to follow-up, n (%)	103 (58.9)	87 (50.6)

NHLBI indicates National Heart, Lung, and Blood Institute; PTCA, percutaneous transluminal coronary angioplasty; and MLD, minimal luminal diameter.

All differences between the two treatment groups are insignificant.

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TABLE 6. Clinical Status at Follow-up

	Fosinopril Patients (N=153)	Control Patients (N=151)
Angina class (CCS) at follow-up, n (%)		
Asymptomatic	118 (77.1)	106 (70.2)
Class I	4 (2.6)	9 (6.0)
Class II	10 (6.5)	14 (9.3)
Class III	6 (3.9)	6 (4.0)
Class IV	15 (9.8)	16 (10.6)
Early (<6 months) repeat coronary angiography, n		
Indication		
AMI	0	0
Angina	19	24
Silent ischemia	5	1
Atypical chest pain	2	2
Syncope	0	1
Management		
Repeat PTCA	19	16
CABG	1	3
Conservative	6	7
PTCA of another lesion	0	2
Repeat PTCA at 6-month visit, n	18	17

CCS indicates Canadian Cardiovascular Society functional class; AMI, acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft surgery.

All differences between both treatment groups are insignificant.

coworkers.[37] As a consequence, restenosis rates calculated according to the most frequently used criteria were also slightly higher in the present study than in MERCATOR, but this observation did not compromise the long-term efficacy of the PTCA procedure. Indeed, although a greater initial gain was followed by a greater loss, the resultant long-term gain was still greater in our study: 22.5% diameter reduction versus 16.9% in MERCATOR. In both studies, these angiographic findings were clinically reflected in similar repeat revascularization rates of approximately 15% during the follow-up period.

Several hypotheses can be formulated to explain why ACE inhibitors fail to prevent restenosis after PTCA. First, the lack of effect on restenosis in clinical studies may be dose related. Indeed, in the rat model, doses up to 70 times higher than in humans have been used. Consequently, it is conceivable that only megadoses of an ACE inhibitor, with unavoidable side effects prohibiting their clinical use, are effective in preventing restenosis. Second, the antiproliferative action of these drugs may be species related. High doses of cilazapril (10 $mg \cdot kg^{-1} \cdot d^{-1}$) and captopril (100 $mg \cdot kg^{-1} \cdot d^{-1}$) have been effective in preventing neointimal proliferation in the rat carotid artery model, whereas in the swine and baboon models, no significant benefit of several ACE inhibitors could be demonstrated.[18-19] Therefore, it seems plausible that rats do not represent the right experimental model for studying the effects of ACE inhibitors on human neointimal proliferation. Finally, it is also conceivable that the muscular response of healthy animal arteries to experimental injury is substantially different from the pathophysiological mechanisms underlying restenosis after therapeutic angioplasty of atherosclerotic human coronary arteries.

Conclusions

Fosinopril, when administered in a dose of 40 mg daily, did not prevent restenosis and did not favorably influence the overall clinical outcome after PTCA even when the treatment was started the day before the procedure. In conjunction with the cilazapril experience, it seems extremely unlikely that, in patients, any beneficial effect on restenosis can be expected from this class of drugs.

Acknowledgments

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Long-term Effects of Angiopeptin Treatment in Coronary Angioplasty

Reduction of Clinical Events but Not Angiographic Restenosis

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Background Angiopeptin is a cyclic octapeptide analogue of somatostatin that has been shown to limit myointimal thickening of arteries in balloon injury models and to restore the vasodilating response to acetylcholine. A randomized, double-blind placebo controlled trial was conducted to assess the effect of angiopeptin in restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA).

Methods and Results Patients received a continuous infusion of either placebo or angiopeptin subcutaneously 6 to 24 hours before PTCA and for 4 days after PTCA (3 mg per 24 hours before PTCA followed by 6 mg per 24 hours after PTCA and for the remaining period). A 1.5-mg bolus dose of placebo or angiopeptin was given at PTCA. Aspirin (acetylsalicylic acid, 150 mg/d) was administered throughout the study period. Coronary angiograms obtained before and after PTCA and at 6-month follow-up were subjected to computerized quantification. Clinical follow-up was performed after 12 months. Primary clinical end points were death, myocardial infarction, coronary artery bypass surgery, or repeat PTCA. In total, 553 patients with 742 lesions were randomized. Clinical follow-up was available for all 553 patients. Angiopeptin decreased the clinical events during 12 months of follow-up from 36.4% in the placebo-treated group to 28.4% in the angiopeptin-treated patients ($P=.046$). Quantitative angiography after PTCA and at follow-up was available in 423 of 455 patients who underwent successful PTCA. The minimal lumen diameter at follow-up was 1.52±0.64 mm in the angiopeptin-treated group compared with 1.52±0.64 mm in the placebo-treated patients ($P=.96$). The late losses were 0.31±0.59 and 0.30±0.62 mm ($P=.81$) and the restenosis rates (>50% diameter stenosis at follow-up) were 36% and 37% ($P=.85$) in the angiopeptin- and placebo-treated groups, respectively.

Conclusions In this study, angiopeptin significantly decreased the incidence of clinical events, principally the rate of revascularization procedures. In contrast, no significant effect was seen on angiographic variables. (*Circulation*. 1995; 91:1689-1696.)

Key Words • growth substances • angina • angioplasty • coronary disease

While various factors such as dissection, thrombus formation, and recoil may affect early results after percutaneous transluminal coronary angioplasty (PTCA), late clinical outcome is thought to be related to vascular smooth muscle cell proliferation and matrix formation, resulting in renarrowing of the lumen of the dilated vessel. This sequence of events constitutes a significant clinical problem and occurs in 30% to 40% of all patients treated.[1-4] Cellular growth is regulated in part by interaction of the cell with proteins and polypeptides in serum. Insulin-like growth factor (IGF-1) has been identified as an important serum and tissue component responsible for cell proliferation in various tissues, including the vascular wall.[5-7] The growth-promoting effect of IGF-1 is potentiated by platelet-derived growth factor (PDGF).[8,9] In addition, fibroblast growth factor increases the binding of IGF-1 to smooth muscle cells, promoting the growth stimulation of IGF-1.[8-10] Angiopeptin, a cyclic octapeptide analogue of somatostatin, prevents an increase in IGF-1 in the vascular wall after balloon injury.[11] Furthermore, angiopeptin inhibits myointimal thickening in balloon-injury models in several animal species at doses similar to those used in PTCA studies in patients.[12-15]

Recently, two double-blind controlled PTCA studies were performed with angiopeptin. In a pilot study in five centers, in which 112 total patients were treated with either placebo or 750 μg/d angiopeptin, the clinical event rate by intention-to-treat analysis at 12 months was lower in the angiopeptin-treated group (25%, compared with 34% in the placebo-treated group), but this difference was not statistically significant.[16] However, a significantly lower angiographic restenosis rate at 6 months was seen in the angiopeptin-treated group (12% versus 40%). In that trial, angiopeptin was administered as in the present study, namely as a continuous subcu-

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taneous infusion for 5 days. In a larger multicenter study of 1246 patients, in which angiopeptin was administered as subcutaneous injections twice per day, there were no statistically significant effects on clinical events or quantitative coronary angiography at follow-up, possibly due to a suboptimal daily dosing regimen.[17] The aim of the present investigation was to evaluate whether the beneficial results of the first pilot study could be confirmed in a larger patient population by use of continuous infusion of angiopeptin. Since data from clinical studies have shown that higher doses of angiopeptin are well tolerated,[17] 6 mg/d angiopeptin was given in the present study.

Methods

Between October 1991 and November 1992, all patients who were scheduled for angioplasty were considered for inclusion at 18 participating centers (see "Appendix"). Eligibility criteria included a patient history compatible with myocardial ischemia and at least one significant coronary stenosis (>50% in diameter). During this study period, 553 patients were randomized to double-blind administration of either angiopeptin or placebo. Active drug was given as a continuous infusion 6 to 24 hours before PTCA (3 mg SC) and a bolus dose of 1.5 mg just before PTCA; the drug was infused at a rate of 6 mg per 24 hours SC on the day of and for 3 days after PTCA. All patients were given a dose of 150 mg aspirin (acetylsalicylic acid) each day throughout the study period. Patients were treated with β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, or long-acting nitrates at the discretion of the investigators. Trial medication was supplied by Henri Beaufour Institute, USA (Washington, DC). Patients were excluded from participation in the study if they had had a recent myocardial infarction (within 4 weeks), severe congestive heart failure, or conditions that precluded follow-up angiography.

The study was approved by the ethics committee at each study center, and written informed consent was obtained from every patient.

Angioplasty Procedure and Follow-up

Balloon angioplasty was performed at each study center according to standard procedures. Selective coronary angiography was performed before PTCA, after PTCA, and at 6 months' follow-up, or earlier if symptoms occurred. Angiograms were recorded to meet the standards for quantitative coronary angiography. Each lesion was viewed in at least two angiographic projections. To achieve maximal vasodilation, each angiogram was preceded by intracoronary injection of 125 to 250 μg nitroglycerin. Angiograms were reviewed at a central angiographic core laboratory and analyzed with an automatic edge-detection algorithm.[18] Acute gain (minimal lumen diameter [MLD] after PTCA minus MLD before PTCA), late loss (MLD after PTCA minus MLD at follow-up) and loss index (late loss divided by acute gain) were calculated from these measurements.

Preprocedural lesion morphology was graded by use of standardized qualitative criteria for eccentricity, length, contour, presence of thrombus, ostial location, angulation, tortuosity, and total occlusion.[19] The presence of postprocedural thrombus or coronary dissection was also recorded according to previously defined criteria.[20,21]

Patients were seen in the outpatient clinic 1 week and 6 months after the procedure for a physical examination, laboratory tests, and an ECG. In addition, at 3, 9, and 12 months, a telephone interview was performed to record clinical events.

End Points

Clinical outcome was analyzed by inclusion of all study patients (intention-to-treat analysis). The primary clinical outcome end point was freedom from major clinical events (death, myocardial infarction, bypass surgery, or repeat coronary angioplasty hierarchical) during the follow-up period. End points were defined as follows: death: all deaths were considered cardiac death; myocardial infarction: the presence of at least two of the following: (1) occlusion of a previously patent coronary artery, (2) prolonged chest pain (≥30 minutes), (3) serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme raised to more than twice the local upper limit for normal, or (4) development of a new Q wave; bypass surgery: emergency or elective coronary bypass surgery involving at least one of the previously dilated lesions; and repeat angioplasty: repeat angioplasty involving at least one of the previously dilated lesions. The decision to perform repeat intervention or bypass surgery was blinded to treatment and based on findings at follow-up angiography in combination with clinical symptoms and the features of myocardial ischemia on ECG or by myocardial scintigraphy.

Angiographic end points were obtained in all patients who had an angiographic follow-up with an analyzable angiogram. The primary angiographic end point was to assess the effect of angiopeptin over placebo on the late angiographic outcome (restenosis) after balloon angioplasty. Restenosis was defined as stenosis of >50% in diameter at angiographic follow-up. Secondary angiographic end points included changes in percent diameter stenosis, follow-up MLD, and late loss.

Statistical Analysis

In the present study, the values for continuous data are expressed as mean±SD, whereas categorical data are reflected by frequencies and corresponding percentages. The differences for continuous data were evaluated by Student's t test, and categorical data were tested by χ^2 test. Event-free survival rates were estimated by the Kaplan-Meier method, and a log-rank test was used to detect difference between groups.

Results

The demographic, clinical, and angiographic characteristics of the 553 randomized patients (278 treated with angiopeptin, 275 with placebo) with 742 total lesions (378 treated with angiopeptin, 364 with placebo) are displayed in Tables 1 and 2. There were no significant baseline differences between groups except for a lower prevalence of bifurcation lesions in the angiopeptin-treated group (14% versus 22%; P=.01). Table 3 shows the flow chart of patients in the study. PTCA was unsuccessful or not performed as planned in 98 patients (44 treated with angiopeptin, 54 with placebo). Emergency bypass surgery or stent implantation was necessary in 24 patients (12 treated with angiopeptin, 12 with placebo), and elective surgery was necessary in 13 (3 treated with angiopeptin, 10 with placebo). Twenty-five patients with unsuccessful PTCA (13 treated with angiopeptin, 12 with placebo) were treated medically. In addition, 4 patients (all treated with placebo) who had a "successful" procedure by visual assessment were excluded on the basis of an inadequate angiographic result by quantitative analysis.

Taking into account patients who refused follow-up angiography or had a technically inadequate film (20 treated with angiopeptin, 7 with placebo), 423 patients with 538 total lesions were used for final angiographic analysis. Clinical follow-up, on the other hand, was obtained in all 553 patients.

Success rates for all attempted cases as assessed visually were 89.7% for angiopeptin-treated patients versus 87.7% for placebo-treated patients. The magnitude of lumen improvement was similar in both treatment groups, and no difference was noted in postproce-

Table 1. Demographics and Clinical Characteristics of the Total Patient Population

	Patients			
	All (n=553)	Placebo-Treated (n=275)	Angiopeptin-Treated (n=278)	P
Age, y (mean±SEM)	58±9	58±9	58±9	.62
Male sex, %	76	79	73	.10
Unstable angina, %	20	19	21	.56
Prior myocardial infarction, %	42	42	42	.95
Canadian heart class, %				
I	10	8	12	
II	38	40	35	
III	37	37	38	
IV	14	13	14	
Hypertension, %	38	36	40	.44
Congestive heart failure, %	3	2	4	.13
Cholesterol, mg/dL (mean±SD)	237±43	237±41	237±44	.94
Diabetes mellitus, %	10	10	10	.92
History of smoking, %	22	20	24	.20
Prior PTCA, %	11	10	12	.29

PTCA indicates percutaneous transluminal coronary angioplasty.

dural lumen diameter (P=.70) or postprocedural percent stenosis (P=.97) (see Table 4).

Late Clinical and Angiographic Results

A primary clinical end point occurred in 28.4% of angiopeptin-treated patients and in 36.4% of placebo-treated patients during the 12-month follow-up period (P=.046). The relative risk for the angiopeptin group was 0.78, with a 95% confidence interval of 0.61 to 1.00 (Table 5). Patient-based analysis of the clinical end points revealed target-vessel PTCA to be the most frequently occurring event (n=108; 14.7% in the angiopeptin-treated group versus 20.7% in the placebo-treated group; P=.03). Coronary artery bypass surgery was performed in 29 patients (10.4%) in the angiopeptin-treated group and in 27 (9.8%) in the placebo-treated group (P=.81). The mortality rates during the 12-month follow-up period were 1.4% and 1.8% (P=.54) in the angiopeptin- and placebo-treated groups, respectively. Myocardial infarction occurred in 1.8% of the angiopeptin-treated patients versus 4.0% of the placebo-treated patients (P=.18) during the follow-up period. Fig 1 shows the cumulative event-free survival rates for the primary clinical end points over time in both groups. Fig 1 (top) shows the event-free survival rate, including target-vessel revascularization, death, and myocardial infarction, whereas Fig 1 (bottom) includes all revascularizations in addition to death and infarction. There were more adverse reactions in the angiopeptin-treated group than in the placebo-treated group. The most

Table 2. Preprocedural and Postprocedural Lesion Morphology in Patients Undergoing Successful Percutaneous Transluminal Coronary Angioplasty

	Lesions, %			
Characteristics	Total (n=742)	Placebo-Treated Group (n=364)	Angiopeptin-Treated Group (n=378)	P
Vessel				.33
Left anterior descending artery	47	49	44	
Left circumflex artery	24	22	27	
Right coronary artery	28	28	28	
Saphenous vein graft	1	1	1	
Length ≥10 mm	33	31	34	.49
Eccentricity	59	59	60	.38
Bend ≥45°	34	32	36	.32
Irregular contour	46	42	49	.09
Calcification	2	1	3	.13
Total occlusion	4	4	5	.57
Ostial	1	2	1	.72
Bifurcation	18	22	14	.01
Thrombus	6	5	8	.17
Proximal tortuosity	12	12	12	.89
Postprocedural dissection*				.15
A	1	1	2	
B	1	0	2	
C	10	10	10	
D	0	0	0	
Postprocedural thrombus	14	12	15	.13

*See Reference 21.

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TABLE 3. Patient Flow for 6-Month Angiographic Follow-up and 12-Month Clinical Follow-up

Patients	Group: Placebo-Treated	Group: Angiopeptin-Treated
Enrolled, n	275 (364)	278 (373)
Inclusion criteria not met	4	5
No lesion or PTCA not attempted	12	11
Failed PTCA, emergency CABG or stent	12	12
Elective CABG	10	3
Medical treatment (failed PTCA)	12	13
Unsatisfactory PTCA result	4	0
Death during first 6 months	1	4
6-Month angiogram, n	220 (291)	230 (309)
Refused angiogram	2	13
Inadequate film	5	7
Completed QCA	213 (266)	210 (272)
12-Month clinical follow-up, n	275	278
Death	6	4
Loss to follow-up	0	0
Completed 12-month follow-up	269	274

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; and QCA, quantitative coronary angiography. Values in parentheses indicate number of lesions.

frequent adverse experiences were gastrointestinal disturbances (Table 6).

Table 4 summarizes the quantitative coronary angiographic findings. The minimal lumen diameter at follow-up was 1.52±0.64 mm in the angiopeptin-treated group, compared with 1.52±0.64 mm in the placebo-treated group (P=.96). The percent stenosis was also similar (45±21% versus 45±20%, P=.70). The restenosis rates (>50% diameter stenosis) were 36% versus 37% in the angiopeptin- and placebo-treated groups, respectively (P=.85). The late loss was 0.31±0.59 mm in the angiopeptin-treated group and 0.30±0.62 mm in the placebo-treated group (P=.81). The cumulative frequency-distribution curve of percent diameter stenosis at follow-up is shown in Fig 2.

A significant correlation was found between restenosis rates and length of angiopeptin pretreatment (P<.05). A longer pretreatment period resulted in a higher rate of angiographic success.

Discussion

Rationale for Angiopeptin Treatment

Angiopeptin is hypothesized to prevent myointimal thickening after vessel injury mainly by inhibition of secretion of growth factors involved in smooth muscle cell proliferation. In addition, the intercellular signal transduction induced by growth factors whose receptors contain an intracellular tyrosine kinase may be inhibited.[22] These growth factors include IGF-1, PDGF, epidermal growth factor, and basic fibroblast growth factor (bFGF). IGF-1 is a crucial progression factor for smooth muscle cell proliferation. PDGF and bFGF increase IGF-1 receptors on smooth muscle cells, and this increase in IGF-1 receptors is needed for the mitogenic effect of IGF-1 on smooth muscle cell proliferation.[10] Balloon injury of arteries causes an increase in IGF-1 and mRNA for IGF-1 in the vascular wall.[7,11] This increase in IGF-1 after balloon

TABLE 4. Angiographic Findings of Patients Undergoing Successful Angioplasty

	Lesions: Total (n=538)	Lesions: Placebo-Treated Group (n=266)	Lesions: Angiopeptin-Treated Group (n=272)	P
Reference diameter, mm				
Before angioplasty	2.75±0.58	2.74±0.61	2.76±0.56	.75
After angioplasty	2.74±0.55	2.73±0.57	2.76±0.54	.58
Follow-up	2.77±0.52	2.77±0.54	2.78±0.51	.69
Minimal lumen diameter, mm				
Before angioplasty	0.95±0.38	0.95±0.39	0.95±0.38	.99
After angioplasty	1.82±0.46	1.82±0.48	1.83±0.43	.70
Follow-up	1.52±0.64	1.52±0.64	1.52±0.64	.96
Percent stenosis				
Before angioplasty	65.0±12.8	64.8±13.0	65.3±12.8	.66
After angioplasty	33.3±11.4	33.4±12.1	33.3±10.6	.97
Follow-up	45.0±20.7	45.4±20.4	44.7±21.2	.70
Restenosis ≥50%, %	36.4	36.8	36.0	.85
Acute gain, mm	0.87±0.47	0.86±0.47	0.88±0.47	.63
Late loss, mm	0.31±0.61	0.30±0.62	0.31±0.59	.81
Loss index	0.36±0.64	0.36±0.63	0.36±0.65	.99

injury in rabbits is prevented by administration of 20 $\mu g \cdot kg^{-1} \cdot d^{-1}$ angiopeptin.[11] A further mechanism may be dephosphorylation of the phosphorylated tyrosine kinase by angiopeptin-induced activation of a membrane-bound phosphatase.[23]

Data are also available from morphometric studies of the coronary arteries of pigs,[12] the aorta and iliac arteries of rabbits[13] and in the aorta[15] and carotid arteries of rats.[14] In rabbits, in vivo administration of 2, 20, and 200 $\mu g \cdot kg^{-1} \cdot d^{-1}$ angiopeptin inhibited myointimal thickening.[23] The lack of a dose-response curve in vivo for myointimal thickening is in contrast to the in vitro dose-response curves obtained in explants of pig coronary arteries[24] and rat carotid arteries.[25]

Postponing treatment for 8 hours after balloon injury decreases the efficacy of angiopeptin, and a delay of 18 hours completely abolishes the inhibitory effect of angiopeptin on myointimal hyperplasia.[13] In contrast, total duration of treatment seems to play a minor role; 2 days of treatment with angiopeptin showed the same inhibition of myointimal thickening as obtained after 5 and 21 days of treatment.[13]

Previous Double-Blind Randomized Trials

In one study,[16] 112 patients were randomized to continuous infusion of angiopeptin (750 μg/d SC) or placebo infusion given the day before balloon angioplasty and for 4 days thereafter. A bolus dose of 375 μg angiopeptin or placebo was administered just before the procedure. Follow-up of clinical events was performed 12 months later, and follow-up angiography was performed 6 months after the procedure. The clinical event rate was reduced at 12 months from 34% in the placebo-treated group to 25% in the angiopeptin-treated group. Owing to the small number of patients in this pilot study, this 26% difference did not reach statistical significance. By use of a binary angiographic end point (>50% diameter stenosis), restenosis was significantly reduced in lesions treated with angiopeptin (12%, versus 40% in the placebo-treated patients; $P=.005$). Late lumen loss was also reduced (0.12 ± 0.46 mm in the angiotensin-treated group versus 0.52 ± 0.64 mm in the placebo-treated group, $P=.003$), and, consequently, repeat revascularization was required less frequently in angiopeptin-treated patients (11% versus 32% in the placebo-treated group; $P=.027$).

These promising findings were not corroborated in a large study comprising 1246 patients, in which angiopeptin was administered as two subcutaneous injections per day instead of as a continuous subcutaneous infusion.[17] In this trial, patients taking three different dosages (5, 20, and 80 $\mu g \cdot kg^{-1} \cdot d^{-1}$ SC BID) of angiopeptin were compared with placebo-treated patients. No statistically significant effect could be demonstrated in the angiographic or clinical parameters with any of the dosages of angiopeptin, although a lower clinical event rate was seen in all three angiopeptin-treated groups compared with the placebo-treated group. One possible explanation for the discrepancy between these two studies might be the short half-life of angiopeptin (90 minutes): Given this half-life, two subcutaneous injections per day might be insufficient, and sustained plasma levels may be needed for longer periods than provided by the two daily injections. In addition, patients were not pretreated with angiopeptin for any substantial period in this study.

Dosage and Duration of Treatment

In animal models, no close dose-response relation has been found with angiopeptin, which has had the same efficacy on myointimal thickening at dosages ranging from 2 to 200 $\mu g \cdot kg^{-1} \cdot d^{-1}$. In the first clinical, randomized angiopeptin trial (pilot study) for restenosis prevention,[16] a medium dose (≈ 10 $\mu g \cdot kg^{-1} \cdot d^{-1}$) was chosen primarily for patient safety. At the start of the present trial, pharmacodynamic properties of angiopeptin in humans were insufficiently known, but it was decided that this trial would use a higher dose than the first study. Due to these circumstances and insufficient knowledge regarding dosage and efficacy in vivo, the finding was not unexpected that the increase in the dosage of angiopeptin did not enhance the efficacy of the treatment from that seen in the pilot study of 112 patients who were treated with a dosage that was eight times lower.[16]

Another crucial question is the length of the treatment period before balloon dilatation. In animal models, lack of pretreatment has been shown to result in loss of therapeutic efficacy.[13] The reason for this may be that the decline in IGF-1 after treatment with angiopeptin occurs over several days, in part owing to the long half-life of IGF-1. This is consistent with findings from previous human studies. In the first study with a positive outcome,[16] pretreatment duration was 24 hours, whereas in a study with a negative result,[17] the first injection was given shortly before balloon angioplasty. In the present study, a significant correlation was found between the restenosis rate and the length of pretreatment. Thus, 24-hour pretreatment may be considered preferable, given previous experiences with animals and humans.

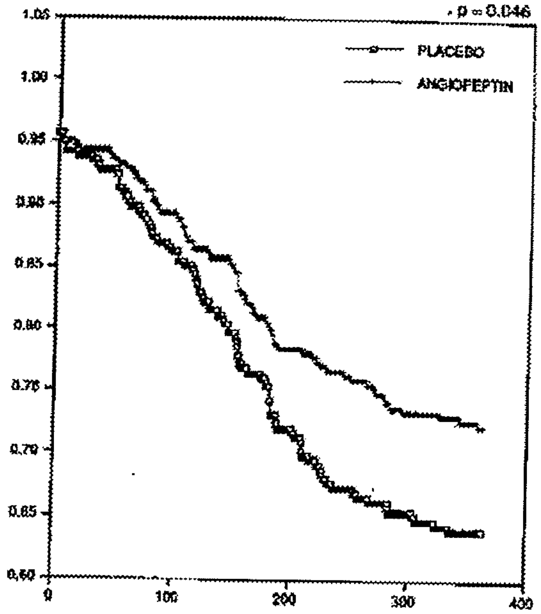
Discrepancy Between Clinical and Angiographic Results

The biological process that occurs after coronary angioplasty is myointimal hyperplasia, and it was there-

Table 5. Incidence of Clinical Events at 12 Months (Hierarchical)

	Events					
Patient-Based Clinical Event	Total (n=553)	Placebo-Treated Group (n=275)	Angiopeptin-Treated Group (n=278)	Odds Ratio	95% Confidence Interval	P
Total	179 (32.4)	100 (36.4)	79 (28.4)	0.69	0.49-0.99	.046
Death	9 (1.6)	5 (1.8)	4 (1.4)	0.79	0.21-2.97	.724
Myocardial infarction	16 (2.9)	11 (4.0)	5 (1.8)	0.44	0.15-1.28	.133
Coronary bypass surgery*	56 (10.1)	27 (9.8)	29 (10.4)	1.07	0.62-1.86	.811
Repeat coronary angioplasty*	98 (17.7)	57 (20.7)	41 (14.7)	0.66	0.43-1.03	.068

*Target vessel.



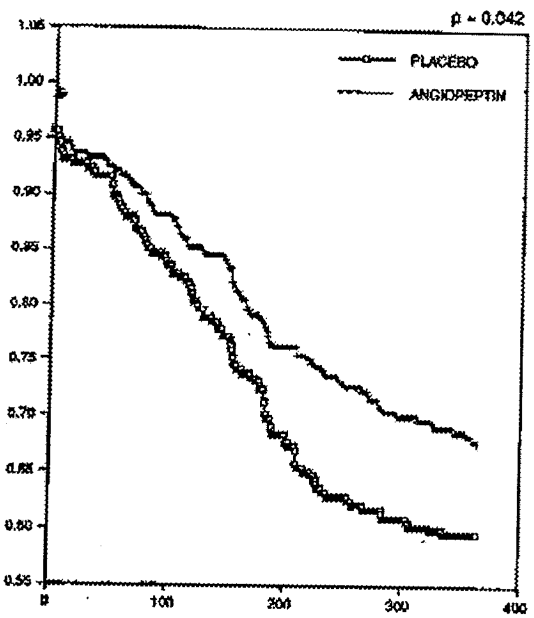


FIG 1. Graphs showing proportion of patients who survived without events at 12 months (no death, myocardial infarction, or target vessel revascularization) (top). Bottom graph also includes patients who underwent non-target vessel revascularization procedures. All patients included (n = 553). Note that the y axis is from 0.55 to 1.05.

fore not unexpected that repeat PTCA was the most common clinical event in this trial. It has been generally assumed that an improvement in clinical outcome after PTCA treatment would be related to prevention of the recurrence of stenosis in the treated vessel. The difference in the clinical event rates between the treatment groups was mainly due to a reduction in PTCA. This discrepancy between clinical and angiographic variables may seem inconsistent and contradictory. However, there could be several potential explanations for these results. In this study, standardization of the angiographic procedure was exercised as previously described.[26] The analysis was performed in a dedicated core laboratory according to current standards, and the participating study centers practiced quality control. On the other hand, the limitations of quantitative coronary angiography must be emphasized, in particular, the difficulties of using the technique to accurately represent three-dimensional morphology of the lesion. There is a possibility that the lack of difference in angiographic restenosis to some extent reflects the inherent inability of angiography to detect small differences in minimal lumen diameters.[27] Intravascular ultrasound imaging might have been a more appropriate method for evaluation of stenosis severity in the present study. It has recently been demonstrated that intravascular ultrasound imaging assessed the presence and severity of coronary lesions more accurately than did coronary angiography.[28]

TABLE 6. Gastrointestinal Side Effects

	Patients, %	
Side Effect	Placebo-Treated (n=275)	Angiopeptin-Treated (n=278)
Nausea	5	10
Diarrhea	3	21
Vomiting	2	6
Flatulence	1	1
Stool abnormality	6	5
Dyspepsia	0	4

Another possible explanation may be that although angiopeptin did not affect the angiographic results, it could affect the regeneration process after balloon dilatation in a way that could beneficially influence function and remodeling of the vessel. A recent experimental study in rabbits showed that the balloon-injured aorta from rabbits receiving angiopeptin by continuous infusion for 2 weeks responded to acetylcholine with vasodilation. This was not the case for the placebo-treated animals.[29] These data suggest that improvement of neoendothelial function after angiopeptin treatment may beneficially affect the physiological role of the treated vessel. This effect is not necessarily related to the degree of myointimal proliferation and may not be reflected by morphological methods, eg, coronary angiography.

Finally, one reason for the lower incidence of clinical events after angiopeptin without concomitant angiographic changes might be a beneficial extracoronary effect of angiopeptin. However, no such effects have yet been documented in humans, and given the short treatment period in this study, this mechanism seems less likely.

Since 13 angiopeptin-treated patients (versus only 2 in the placebo-treated group) refused follow-up angiography, it could be argued that performing additional angiograms in the angiopeptin-treated group might have stimulated more repeat revascularizations. However, this seems unlikely for several reasons. Repeat angio-

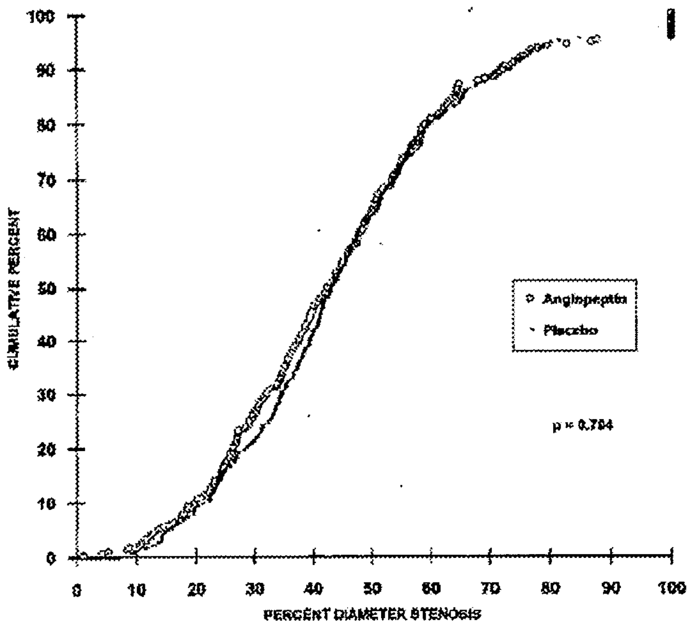


FIG 2. Graph showing cumulative frequency distribution of percent diameter stenosis at follow-up.

plasty was clinically driven either by angina or by a positive exercise tolerance test. Furthermore, patients who did not return for angiographic follow-up were likely to be free of clinical symptoms. Coronary angiography in these patients thus would have increased the difference in clinical events between the treatment groups.

Conclusions

This study demonstrated that when angiopeptin treatment was started 6 to 24 hours before PTCA, it significantly decreased the incidence of clinical events. On the other hand, no significant effect on angiographic variables was seen. There could be various explanations for these findings, such as the method of quantitative coronary angiography not being sensitive enough to detect small differences between the two treatment groups or hitherto unrecognized mechanisms of action for angiopeptin. In future studies with angiopeptin, the pretreatment period should be at least 24 hours. A lower dose than was used in the present study may be equally effective. Intravascular ultrasound imaging, a diagnostic method complementary to quantitative coronary angiography, may assist in the evaluation of morphological changes in the coronary arteries.

Appendix

European Angiopeptin Study Group: Study Coordinator: Håkan Emanuelsson; Steering Committee: Jens Peder Bagger, Raphael Balcon, William E. Battle, Kevin J. Beatt, Håkan Emanuelsson, Marie Foegh, and Merete Holm Bentzen.

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Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study)

The ERASER Investigators*

Background—Although stents reduce restenosis compared with balloon angioplasty, their long-term efficacy is limited by neointimal hyperplasia. Platelet and $\alpha_v\beta_3$ integrin receptor inhibition limits neointimal proliferation in animal models of arterial injury.

Methods and Results—We tested whether the dual β_3 integrin blocking agent abciximab, administered for 12 or 24 hours at the same intravenous dose as that shown to reduce adverse clinical events (death, infarction, and revascularization) after angioplasty, would reduce restenotic tissue volume, as measured by intravascular ultrasound at 6 months. Two hundred twenty-five patients were randomly allocated to placebo or abciximab before coronary intervention. Of the 215 patients who received stents and study drug, 191 (88.8%) returned for late (≥4 months) coronary evaluation. Tissue volume, expressed as a percentage of stent volume, did not differ: 25±13%, 27±15%, and 29±14% for the patients in the placebo and the 12- and 24-hour abciximab groups, respectively. Lack of abciximab benefit was confirmed by quantitative coronary angiography (dichotomous restenosis: 11.6%, 18.9%, and 19.4%; loss index: 0.33, 0.52, and 0.47, respectively, P=NS).

Conclusions—Potent platelet inhibition with abciximab, as administered in this study, does not reduce in-stent restenosis. The interrelationship between stents, platelets, and neointimal proliferation requires further study. (*Circulation.* 1999;100:799-806.)

Key Words: angioplasty ■ stents ■ platelets ■ glycoproteins ■ vitronectin

Intracoronary stents reduce the absolute incidence of restenosis compared with balloon angioplasty in selected patients and lesions by 10% to 15% and improve 6-month event-free survival by 10% to 19%.[1,2] Stents reduce restenosis by an improvement in initial lesion cross-sectional area, but stenting aggravates the neointimal hyperplasia and the late lumen loss compared with that after angioplasty alone.[1]

Reduction of neointimal hyperplasia after stent placement should greatly retard clinical restenosis. Schwartz et al[3] and Miller et al[4] described the chronology of in-stent restenosis in animal models as early thrombosis, followed by thrombus endothelialization and infiltration by lymphocytes and monocytes, and finally smooth muscle cell migration into the resolving thrombus and proliferation. Ligand binding to $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) and $\alpha_v\beta_3$ (vitronectin) receptors mediates platelet aggregation and smooth muscle cell migration, respectively, both of which appear to be involved in the restenosis process.[5] Combined inhibition of both integrins,[6] specific inhibition of $\alpha_v\beta_3$,[7-11] and profound antibody-induced thrombocytopenia[12] inhibit neointimal thickening after arterial injury in animal models. Abciximab inhibits both integrins and has been shown to decrease the incidence of target lesion revascularization (TLR) after angioplasty.[13] Abciximab also cross-reacts with the leukocyte integrins Mac-1 and intracellular adhesion molecule-1, which mediate inflammation after arterial injury and may be involved in restenosis.[14,15]

We hypothesized that intravenous abciximab might diminish neointimal hyperplasia after intracoronary stenting in humans. This study was designed to test that hypothesis, determining neointimal hyperplasia by measuring in-stent volume obstruction by 3D arterial reconstruction of intravascular ultrasound (IVUS) images.

Methods

Study Design and Study Population

The Evaluation of ReoPro® And Stenting to Eliminate Restenosis (ERASER) study was a double-blind, placebo-controlled randomized trial carried out at 17 institutions. Patient enrollment began May 16, 1996, and was completed February 17, 1997. The protocol was approved by the institutional review board at all sites. Eligible patients provided written informed consent. Patients were required to have a de novo target coronary artery stenosis of ≥50% in a vessel of diameter 2.75 to 3.5 mm and to be referred for intracoronary stent implantation with an (expected single) 15-mm Palmaz-Schatz stent. Patients were excluded if they had a myocardial infarction within 72 hours before randomization, evident intracoronary thrombus, previous coronary intervention on a nontarget lesion within the past 6 months, planned debulking before stent placement, expected inability to access the

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TABLE 1. Demographics

	Intention to Treat			Primary Analysis		
	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
No. of patients	71	79	75	60	66	66
Age, y, median (IQR)	59 (50,67)	62 (54,72)	58 (50,68)	58 (50,67)	61 (54,71)	58 (50,67)
Female, %	22.5	25.3	16.0	21.7	22.7	15.2
Diabetes, %	11.3	12.7	18.7	8.3	13.6	16.7
Hypertension, %	50.7	46.8	52.0	46.7	45.5	50.0
Smoker (current or quit within 1 y), %	28.2	29.1	36.0	28.3	30.3	39.4
Prior PCI, %	16.9	12.7	12.0	16.7	13.6	12.1
CCS Angina Class, %						
I-II	33.8	22.8	30.7	33.4	25.8	25.7
III-IV	52.2	55.7	62.7	53.3	57.5	66.7
Time to follow-up, d, median (IQR)	197 (184,211)	193 (184,213)	191 (185,214)	194 (184,209)	193 (185,213)	190 (185,212)

IQR indicates interquartile range; PCI, percutaneous coronary intervention; and CCS, Canadian Cardiovascular Society.
All $P>0.10$.

target lesion by IVUS (eg, calcified plaque, tortuous vessel), or standard contraindications to the use of abciximab.[13]

Randomization and Drug Regimen

Patients were randomized after the target lesion had been identified by angiography and before first device activation into 1 of 3 groups by sealed envelopes provided by the coordinating center. The physicians involved with the procedure remained blinded to study drug. The treatment regimens were (1) placebo bolus+2 consecutive 12-hour placebo infusions; (2) abciximab 0.25 mg/kg bolus+0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (up to 10 μg/min maximum) continuous infusion for 12 hours followed by 12-hour placebo infusion; or (3) abciximab 0.25 mg/kg bolus+2 consecutive 12-hour 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (up to 10 μg/min maximum) infusions. Patients received ≥200 mg oral aspirin ≥2 hours before the procedure and intravenous heparin titrated to an activated clotting time of 250 to 300 seconds. Aspirin was to be continued for ≥6 months. It was strongly recommended that heparin be discontinued immediately on the completion of the procedure to allow removal of arterial sheaths 4 to 6 hours later. When heparin was continued for clinical indications, it was to be titrated to an activated partial thromboplastin time between 50 and 70 seconds. Ticlopidine use was left to the investigator's discretion. Patients received nitroglycerin 100 to 300 μg IC immediately before preintervention, postintervention, and follow-up angiograms and IVUS interrogations.

TABLE 2. Baseline Angiographic Data: Primary Analysis Population

	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
Lesion location, %			
LAD	50.0	51.5	48.5
LCx	21.7	16.7	19.7
RCA	28.3	31.8	31.8
Lesion length, mm, median (IQR)	9 (7,13)	10 (7,12)	11 (7,14)
Calcification, moderate-severe, %	13.4	12.2	12.1
Total occlusion, %	6.7	4.5	3.0
Thrombus present, %	1.7	1.5	3.0
Modified ACC lesion classification B_2 or C, %	40.0	36.4	48.4

LAD indicates left anterior descending; LCx, left circumflex; RCA, right coronary artery; IQR, interquartile range; and ACC, American College of Cardiology.
All $P>0.10$.

Stent Implantation Procedure

Stent implantation was performed according to routine clinical practice, aiming for an "optimal" result. To standardize the measurements, a single 15-mm Palmaz-Schatz stent was planned in all cases. If clinically indicated, a second stent could be placed in series with the first. Postdilatation to ≥14 atm was strongly recommended. IVUS guidance was used to confirm optimal placement or suggest further dilatations. The MUSIC criteria (complete stent apposition, symmetrical expansion, and adequate in-stent cross-sectional dimension[16]) were used to define adequate stent expansion.

Follow-Up Evaluation

Patients were discharged from hospital after completion of study drug infusion and being deemed clinically stable. In-hospital testing included electrocardiography before treatment, at the completion of the stent procedure, and at hospital discharge; platelet count before study drug infusion, at 2, 12, and 24 hours after initiation of study drug, and at hospital discharge; and creatine kinase with MB isoenzymes ≤2 hours before study drug administration and at 8, 16, and 24 hours.

Patients were asked to return for follow-up at 6 months for an assessment of clinical status, electrocardiography, angiography, and IVUS. If the patient required revascularization of the target lesion earlier, angiography and IVUS were to be performed at that time. These results were used as the 6-month results. If stent occlusion occurred within the first 30 days, the patient was excluded from evaluation for the primary efficacy end point. Coronary angiography performed earlier than 4 months was not used for end-point determination unless restenosis or TLR was documented.

Quantitative IVUS and Angiography

Three IVUS systems were used: Cardiovascular Imaging Systems, Hewlett-Packard and Boston Scientific Corp, and Endosonics. The same instrument type was used for poststent and follow-up imaging.

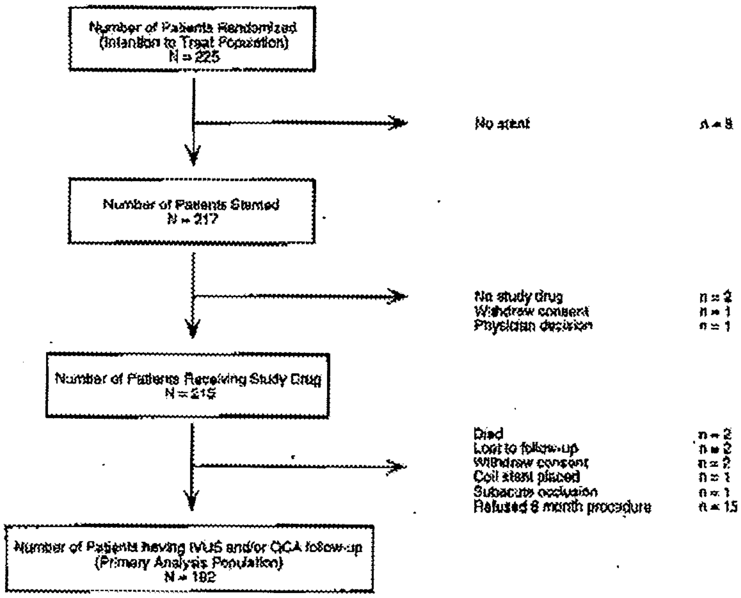

Figure 1. Patient flow in the ERASER study.

Results from the 3 instruments would be expected to be similar.[17] The IVUS examination was performed with motorized pullback of the ultrasound catheter at 0.5 mm/s beginning ≥1 cm distal and continuing to ≥1 cm proximal to the stent(s) with videotape recording.

Ultrasound analysis was performed by the Cardialysis IVUS Core Laboratory by investigators blinded to clinical treatment. A maximum of 200 IVUS images were digitized at a user-defined digitization frame rate (maximum 20 images/s). A minimum-cost algorithm was applied for the automated contour detection of the intimal leading edge and the intracoronary stent boundary. Segments of 3 to 5 mm immediately proximal and distal to the stent were taken as reference diameter. In these segments, the intimal leading edge and external boundary contours (plaque-media) were determined by the algorithm.

Quantitative ultrasound measurements included diameter (mm) and area (mm^2) in both the stent and the reference segments. Volumes of the stent, lumen, and intimal hyperplasia are calculated as

$$V = \sum_{i=1}^{N} A_i \times H,$$

where V is volume, A is area of lumen or stent in a given cross-sectional ultrasound image, H is slice thickness, and N is number of digitized cross-sectional images encompassing the volume to be measured. In-stent volume obstruction percent is determined as intimal hyperplasia volume divided by total in-stent volume times 100.[13–20] Intraobserver and interobserver differences in volumetric measurement (nonstented segments) have been reported (n=30; r=0.99).[21]

Angiographic Measurements

Off-line quantitative coronary angiographic (QCA) analysis was performed at the Washington (DC) Hospital Center Angiographic Core Laboratory by investigators blinded to clinical treatment.

TABLE 3. Treatment

	Intention to Treat			Primary Analysis		
	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
Maximum ACT, s (IQR)	328 (284,376)	335 (302,415)	338 (307,385)	324 (285,375)	330 (302,419)	340 (309,385)
Completed >12 hours of study drug infusion, %	96.0	96.9	96.6	95.0	96.9	96.9
Completed full infusion of study drug infusion, %	84.6	90.3	92.5	95.0	93.8	92.4
Number of stents placed at target lesion, %						
0	1.4	6.3	2.7	0.0	0.0	0.0
1	83.1	78.5	73.3	85.0	83.3	74.2
2	12.7	12.7	20.0	13.3	13.6	21.2
>2	2.8	2.5	4.0	1.7	3.0	4.5
Angiographic complications, %	16.9	13.9	20.0	15.0	13.6	19.7

ACT indicates activated clotting time; IQR, interquartile range. Procedural complications include new thrombus, distal embolization, major dissection, minor dissection, transient occlusion, reduction in TIMI flow from 3 to 2, local perforation, tamponade, side-branch occlusion, other vessel inclusion, spasm, and unsatisfactory stent deployment.

All P>0.10.

TABLE 4. Clinical Outcome

	Intention to Treat			Primary Analysis		
	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
Event rate through hospital discharge						
Composite of death, MI, or TLR, %	11.3	5.1	9.3	10.0	6.1	9.1
Death	0	0	0	0	0	0
MI	11.3	5.1	9.3	10.0	6.1	9.1
TLR*	1.4	0	0	0	0	0
TIMI major bleed, %	1.4	3.8	1.3	1.7	1.5	1.5
Event rate through 6 months						
Composite of death, MI, or TLR, %	25.4	20.9	22.7	25.0	24.2	24.2
Death	2.8	0	0	0	0	0
Any MI	12.7	7.6	9.3	11.7	9.1	9.1
Q wave MI	2.8	3.8	1.3	3.3	4.5	1.5
TLR*	15.5	13.9	13.3	16.7	16.7	15.2

MI indicates myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

*All patients had a repeat percutaneous coronary intervention as the reason for TLR; no patient had coronary artery bypass surgery.

All P>0.10.

Cineangiograms were acquired at the clinical sites in multiple, matched projections before and after stent placement and at 6-month follow-up. Standard morphological criteria were used to characterize baseline lesion complexity[22] and angiographic complications.[23]

Cine frames were selected from the 2 "sharpest and most severe" projections of the stenosis before and after stent placement and at late follow-up; sequential cine frames were matched for their position within the cardiac cycle. QCA used the CMS-GFT algorithm.[24] Binary restenosis was defined as a >50% diameter stenosis at follow-up.

Definitions and End Points

The primary efficacy criterion for the trial was defined as percent in-stent volume obstruction of the target lesion, measured at 6 months by IVUS. Primary safety objectives were defined as major bleeding[25] not associated with bypass surgery through discharge or 7 days, whichever occurred first, and mortality and intracranial hemorrhage through 6 months. Secondary efficacy objectives were defined as target lesion mean and minimum lumen diameter (MLD), late loss and loss index by QCA at 6 months, and a composite of death, myocardial infarction, and TLR within 6 months. Myocardial infarction was defined as (1) new significant Q wave of ≥0.04 seconds or having a depth of ≥25% of the corresponding R wave amplitude in ≥2 contiguous leads or (2) creatine kinase MB ≥3 times the upper limit of normal.

Study Hypothesis and Statistical Analysis

The primary study hypothesis was that either abciximab dosing regimen would diminish in-stent percent volume obstruction compared with placebo. Previous observation suggested an expected in-stent volume obstruction of 38±24% (Gary Mintz, MD, personal communication). To obtain 80% power to detect an absolute 11% difference between treatment groups, 60 patients per group were required. Assuming that 80% of randomized patients would return for an interpretable 6-month IVUS, the total sample size was 225 patients. The study was not powered to show differences in clinical end points. Patients randomized but not treated with ≥1 stents or study drug or who did not return for angiographic or ultrasound follow-up were excluded from the primary efficacy analysis. Intergroup differences were assessed by ANOVA or χ^2 techniques. Grouping of the 2 abciximab groups for analysis of clinical end points was prespecified. A nominal value of P<0.05 was considered

TABLE 5. IVUS: Primary Analysis Population

	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
Mean stent CSA, mm²			
Postprocedure	8.46±2.09 (51)	8.92±2.34 (59)	8.70±2.41 (59)
6-month follow-up	8.49±2.20 (52)	9.13±2.12 (54)	9.10±2.48 (53)
Mean lumen CSA at 6-month follow-up, mm²	6.41±2.27 (52)	6.62±2.58 (54)	6.56±2.46 (53)
Volume obstruction at 6-month follow-up, %*	25.10±14.76 (52)	27.04±15.41 (50)	29.15±14.16 (52)
Minimal lumen CSA, mm²			
Postprocedure	6.84±1.89 (51)	7.14±2.01 (59)	7.07±1.98 (59)
6-month follow-up	4.82±2.06 (52)	4.96±2.40 (54)	4.64±2.06 (53)

CSA indicates cross sectional area.

*In 5 patients who had CSA determined, there were technical difficulties in determining stent length for measurement of % volume obstruction.

All values are mean±SD (n); all P>0.10.

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TABLE 6. QCA: Primary Analysis Population

	Placebo	Abciximab 12-Hour Infusion	Abciximab 24-Hour Infusion
Reference diameter, mm			
Preprocedure	2.94±0.52	2.97±0.45	3.03±0.52
Postprocedure	3.00±0.51	3.06±0.45	3.11±0.52
6 months	3.00±0.49	2.94±0.52	3.09±0.51
MLD, mm			
Preprocedure	0.93±0.44	0.95±0.43	1.03±0.51
Postprocedure	2.72±0.41	2.82±0.42	2.87±0.45
6 months	2.09±0.64	1.96±0.91	2.03±0.68
Target lesion stenosis, %			
Preprocedure	68±14	68±13	66±16
Postprocedure	8±11	7±11	6±13
6 months	30±19	34±27	34±20
In-stent mean luminal diameter at 6 mo, mm	2.72±0.56	2.55±0.93	2.69±0.67
Acute gain, mm	1.80±0.44	1.87±0.53	1.84±0.54
Late loss, mm	0.63±0.58	0.88±0.76	0.80±0.58
Loss index (late loss/acute gain)	0.33±0.45	0.52±0.51	0.47±0.55
In-stent restenosis (≥50%) at 6 months, %	11.6	18.9	19.4

Values are mean±SD.
All P>0.10.

significant. Subset analyses were prespecified only for 3 subgroups: optimal versus suboptimal stent deployment, study drug administration according to protocol or not, and 1 stent at the target lesions versus ≥2 stents.

Results

Baseline Characteristics

Baseline patient and angiographic characteristics are shown in Tables 1 and 2. Patient flow through the study is depicted in Figure 1. There were no intragroup differences in any of the measured characteristics.

Initial Treatment and Outcome

Initial treatments are described in Table 3. Two hundred twenty-two patients (98.7%) received study drug, and 199 (88.4%) completed the study infusion. The median activated clotting time before treatment was 312 seconds. Two hundred seventeen patients (96.4%) received coronary stents. Less than optimal stent deployment by the MUSIC criteria was observed in 45%, 62%, and 67% of the placebo and short and long abciximab groups, respectively (P=NS). Angiographic complications were rare and were equally distributed among the treatment groups.

Clinical Outcomes

Clinical outcomes are described in Table 4. The composite in-hospital end point of death, myocardial infarction, or TLR was seen in 11.3%, 5.1%, and 9.3% in the placebo, short abciximab infusion, and long abciximab infusion groups, respectively. The composite end point of death, myocardial infarction, or TLR at 6 months did not differ among the groups (25.4% placebo versus 21.4% combined abciximab, P=NS). TLR predominated in the composite primary clinical end point and occurred in 15.5% of placebo-treated patients and 13.6% of the combined abciximab-treated group (P=NS).

IVUS and QCA

Data for IVUS and QCA are presented in Tables 5 and 6 and are illustrated in Figures 2 and 3. At the completion of the stenting procedure, the treatment groups were well balanced for angiographic percent stenosis. At follow-up, there was no difference in angiographic outcome, with MLDs of 2.7±0.6, 2.6±0.9, and 2.7±0.7 mm in the placebo, 12-hour, and 24-hour abciximab groups, respectively. When measured by IVUS, with or without imputation for target sites that were occluded or tightly stenosed and could not be crossed by the device (placebo, n=5; 12-hour abciximab infusion, n=5; 24-hour abciximab infusion, n=4), there was no difference in the in-stent percent volume obstruction among the 3 groups (see Figure 3). Follow-up IVUS and QCA measurements of mean luminal diameter (r=0.83) and MLD (r=0.72) were closely correlated. Because of heightened interest engendered by the EPISTENT trial results in diabetics, we also present a post hoc analysis of the primary end-point data, divided into subsets by diabetic status. In-stent volume obstruction for diabetics randomized to placebo was 35±22% (n=3), randomized to 12-hour infusion of abciximab was 27±18% (n=10), and randomized to 24-hour infusion of abciximab was 31±16 (n=13).

Discussion

This study shows that abciximab, given either at the same dose or for the same dose at a longer duration than that which

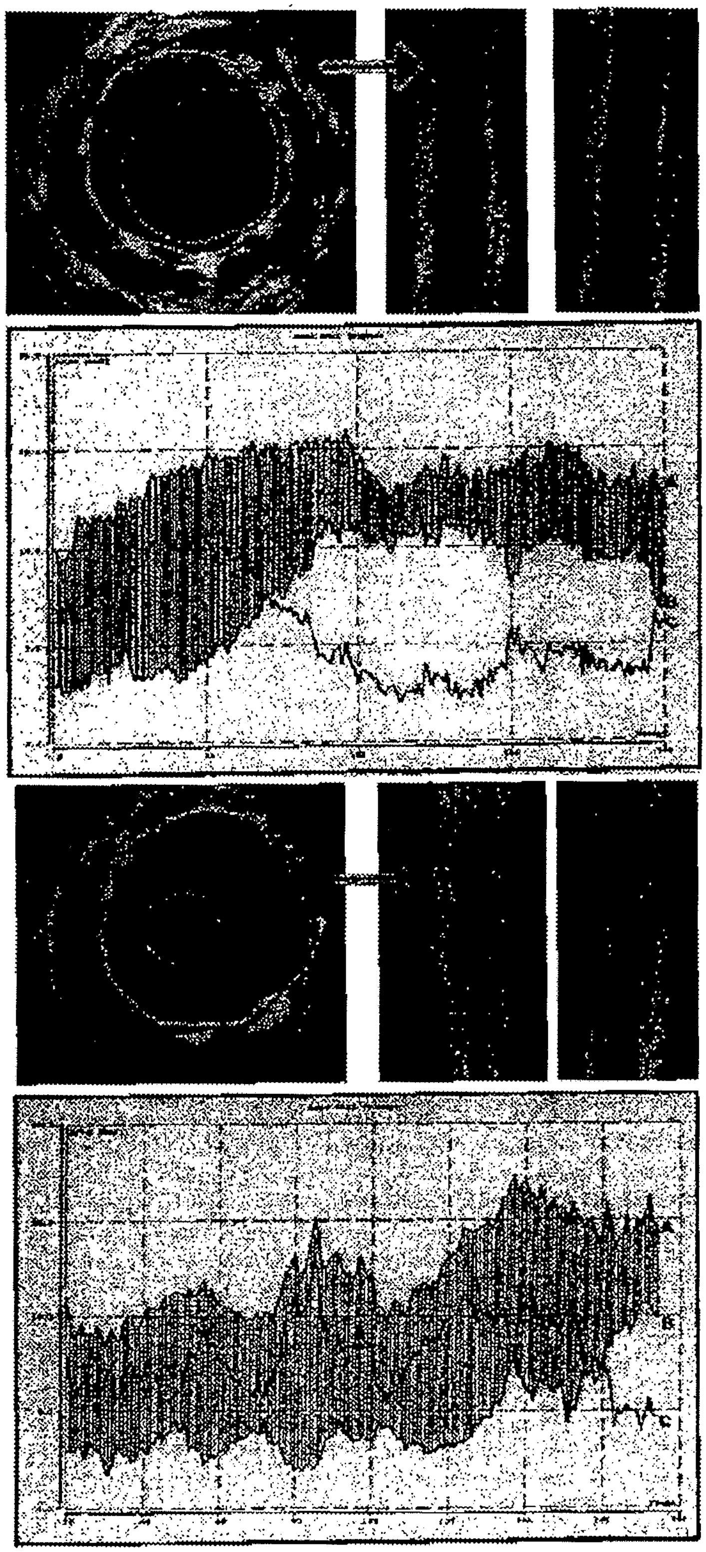

Figure 2. Typical longitudinal IVUS in-stent analysis.

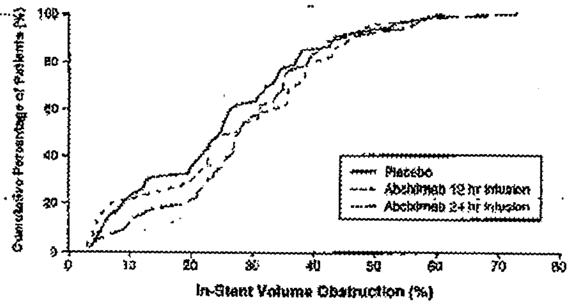

Figure 3. Cumulative distribution of the percent in-stent volume obstruction.

decreased TLR at 6 months from 22.3% to 16.5% (P=0.007) after balloon angioplasty in the EPIC study,[13] does not reduce neointimal volume after stenting.

This observation enhances our understanding of restenosis after stenting by essentially eliminating 1 putative mechanism, organization of platelet-rich thrombus, and improving our understanding of the role of the $\alpha_v\beta_3$ receptor in that process. At the onset of this study, the abciximab dose used was believed to be likely to inhibit the $\alpha_v\beta_3$ receptor, whose KD_{50} (11±3 nmol) is similar to the platelet $\alpha_{IIb}\beta_3$ receptor.[26] Reconciliation of these data suggests that the dose used was too low or asynchronously timed with a maximal $\alpha_v\beta_3$ receptor expression, or that redundant pathways exist to, in a teleological sense, "protect" the wound-healing process. In fact, recent data suggest that $\alpha_v\beta_3$ receptor expression after arterial injury peaks at 7 to 14 days,[27] after high-level receptor inhibition by abciximab, as used in this study, it diminished.[26,28] Unless the late clinical benefit noted in EPIC was due to happenstance alone, one would have to invoke a different set of mechanisms than those tested in the present study.

This was the first clinical trial to use percent volume coronary obstruction assessed by IVUS as a primary study end point. Our results provide insight into the advantages and disadvantages of this end point instead of percent stenosis or MLD as judged by QCA, or instead of clinical events. IVUS-determined 3D neointimal volume was chosen because it most closely reflects the tissue mass of restenosis, it could be easily measured because of the visibility of the stent to IVUS, and its mean/SD ratio would allow a lower sample size with adequate power to detect a plausible biological difference.

Correlations between IVUS and QCA measurements were good. We did not anticipate the relatively large proportion of patients without follow-up IVUS because of the presence of a high-grade coronary stenosis that made passage of the ultrasound device unsafe or impossible (6.5%) or the relatively large proportion of patients with technically inadequate studies (5.6%). Were a therapeutic intervention to decrease restenosis, the imbalance in the number of lesions that could not be restudied because of failure to pass the ultrasound device would necessitate an acceptable method of imputation for this end point to be useful. Miniaturization of the IVUS probe and further clinical experience should diminish these problems in the future. One must question whether a measurement of the volume of neointima itself or one that on the basis of prior QCA studies (percent area stenosis or minimum cross-sectional area)[29,30] may better correlate with adverse clinical events is better suited as a primary end point for such a trial. Notably, the coefficient of variation (SD/mean) for the QCA data was less than for the IVUS data, implying that on a purely statistical basis, QCA has greater power to detect differences in a given patient population than does IVUS. Finally, a sizable proportion of implanted stents did not meet criteria for "optimal" deployment by the MUSIC criteria. These criteria were infrequently achieved in that study also.[16]

Three other factors may influence the interpretation of this study. First, the results should not necessarily be extrapolated to balloon angioplasty because the mechanisms of restenosis differ.[31,32] Second, we cannot exclude a benefit of larger, and possibly longer, infusion doses of abciximab or of a more powerful or longer-lasting $\alpha_v\beta_3$ receptor inhibitor.[33] Finally, the important reduction in periprocedural myocardial infarction with abciximab noted in the EPIC,[13] EPILOG,[34] and EPISTENT studies,[35] with which our data are consistent, must be considered.

Appendix

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